SURGERY, GYNECOLOGY AND OBSTETRICS

AN INTERNATIONAL MAGAZINE, PUBLISHED MONTHLY

VOLUME 62 APRIL, 1936 NUMBER 4

THE VALUE OF RADIATION THERAPY IN THE TREATMENT OF CARCINOMA OF THE BREAST

A CRITICAL ANALYSIS OF PUBLISHED STATISTICS

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IN 1878 Billroth's statistics showed 8 cures in 143 cases of mammary carcinoma —5.6 per cent.

In 1894 Halstead published a description of a radical amputation of the breast, and in the same year Willy Meyer published independently a similar operation. With small modifications the procedure as then described has remained—for four decades—the recognized practice in the treatment of mammary carcinoma.

Many analyses of results have been published, some, such as those of Lane-Claypon, being of great scope and detail. It is interesting to examine these surgical records as a background against which to consider the results obtained by the use of radiation therapy in various forms, and it is significant to do so broadly in two groups: those compiled in the earlier years of the radical operation, and those of later years. In both, the advance on Bilbroth's 5.6 per cent is striking. Tables IA and IB embody the results of an extensive investigation into British, European, and American literature. Different authors employ different methods of grouping their cases. The various figures have been recorded in the manner selected by the authors, but an endeavor has been made to clarify the position by a simultaneous arbitrary classification into the three broad groups of early, late, and total or unclassified. A column has also been added for that group of cases usually classed as inoperable, but perhaps more usefully referred to for our purpose as very advanced.

From the figures tabulated in Table IA it will be seen that in the earlier statistics there is a wide range in the percentage results according to the presence or absence of glandular adenopathy, but that when results are judged on total cases operated on, the average percentage cure is 36.4 at 3 years, and 27.5 at 5 years.

In Table IB some later figures are tabulated. The statistics scarcely better the earlier figures. Taking an average over the combined groups the percentage cure figures are 39.4 and 28.1 at 3 and 5 years, respectively.

A significant figure is published by Greenough, who gives 15 per cent as the 5 year cure for cases treated by incomplete operations, while Lane-Claypon records a difference of 14 per cent in the 3 year figures for complete and incomplete operations, in favor of the former.

Radiation therapy. In considering the place of radiation therapy in carcinoma of the breast, it is important to distinguish between radiation combined with surgery, and radiation alone. A large accumulation of figures is available for the combined technique. In the case of radiation alone, the statistics are more

scanty, but at least sufficient are available to make an interesting survey. It has been thought desirable to deal with X-rays and with radium separately. While the radium figures refer to radium therapy alone, it should, however, be mentioned that in a few cases the X-ray statistics include cases in which radium has been combined with X-ray therapy.

X-ray therapy. The application of X-rays to malignant disease is a relatively recent development. Although the discovery of the X-ray was announced in 1895, and although the new ray was in use in the treatment of mammary carcinoma as early as 1901, little advance was made in deep therapy until in 1914 a new era was introduced by the perfection of the Coolidge tube. Modern deep X-ray therapy may be regarded as having its beginnings at that time. In spite of great advances, the science is even now in its infancy. Techniques are changing from year to year in the light of clinical and laboratory research into the problems of quality, intensity, time-spacing, and sensitivity. Even mechanical development is so rapid that the most modern X-ray installation is quickly out of date. These facts cannot be ignored in a review of the present day results of X-ray therapy.

X-rays combined with surgery. Opinions differ as to the efficacy of surgery plus X-ray therapy as a routine procedure. A wide review of available statistics would seem to be the only means of arriving at a reasoned conclusion. Such a review is incorporated in Tables IIA and IIB. As in Tables IA and IB, the information has been culled from Continental and American, as well as from British, sources, and again a uniform arbitrary classification into early, late, and total cases has been made, while retaining the various groupings selected by the individual authors. No attempt has been made to estimate the relative merits of pre-operative, postoperative, or pre-operative and postoperative X-rays.

Table VI shows at a glance the comparison between modern results with and without X-rays.

It is interesting to note that all radiologists do not proceed on the same principles. So eminent an observer as Regaud, for example, is opposed to the combination of X-rays with surgery as a routine. He advises the preoperative use of X-rays as a means of rendering an inoperable case amenable to surgery, and the reservation of postoperative X-ray therapy for certain areas specifically under suspicion in individual cases, or for actual recurrences. Wintz allows a period of 6 or 8 months to elapse after operation before proceeding with X-ray therapy, unless in the event of earlier development of nodules or gland metastases.

X-ray therapy alone. Sources of information are here more limited, relatively few clinics practicing the method with sufficient frequency and with sufficient stability of technique to enable reliable pronouncements to be made. Nevertheless, it has been found possible to collect some percentage figures from the literature, and these are set forth in Tables IIIA and IIIB. The same method of tabulation has been employed as in the previous tables in order that comparable results may be readily visualized.

For convenience again, Table VI has been drawn up to allow of immediate comparison and contrast of the results of surgery, surgery plus X-rays, and X-rays alone, as obtained by modern technique.

Radium therapy. The isolation of radium was announced to the Academy of Sciences in Paris in 1898. Its application to therapeutics was suggested in 1901. Before the Great War radium centers were beginning to spring up in this country. Already the sensitivity of carcinoma of the breast to the new type of radiation was known, and Finzi, finding difficulty in effecting adequate penetration had visualized its use as an external application when sufficient supplies should become available. Twenty-five years ago, Dominici used radium in the axilla as a postoperative measure.

The greatest advances have taken place in the last decade, and we are now, thanks to the work of Stahel, Sievert, Mayneord, Parker, and many others, in the early years of a new era, in which the amount of energy actually delivered to the tumor and to the tissues will be measured in physical units. The impor-

TABLE IA.—SURGERY ALONE

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Greenough and Simmons Radical operation cures	1894–1904							21	
Westermark (quoting Brattstrom)	1898–1915							23	
Tixier	1902–1914							38	
Westermark (quoting Brattstrom)	1905–1915							25.5	
Greenough, Simmons, and Barney	1907			20.9					
Ochsner	1907			34.7				22.4	
Bloodgood (a) Glands not involved (b) Glands involved (c) Operable, not grouped	1908	85	30	42					
Depage	1908			48					
Greenough and Simmons Radical operation cures	1911–1914							32	
Judd	1912							30	
Lindenberg	1914							28	
Averages		85	30	36.4				27.5	

tance of this development is fundamental. Radium therapy is being lifted from the realm of the empirical to the level of an exact physical science. A wealth of information is becoming available as to the sensitivity (physically determined) of different tumors, and of the same tumor in varying sites; and rapid advance will be assured by the correlation of the effects produced by the γ-rays of radium on a standardized and international scale.

Surgery plus radium. From a study of the methods employed in many different clinics, it is apparent that after radium treatment of cancer of the breast, local or radical amputation is frequently carried out, either as a routine procedure or on account of unsatisfactory resolution. In some clinics radical operation is followed by the application of surface radium applicators to various areas. Wintz carries out a local excision of tumor mass or gland in order to obtain pathological confirmation of the nature of the growth. Various combinations of these procedures are carried out by different workers.

Table IV furnishes an interesting comment upon this aspect of the problem. It incorporates the only available figures bearing directly upon this section. Both sets of figures refer to the implantation of radium at the time of operation. This method is often criticized on the ground of delayed healing. The criticism would appear, however, to be valid only in so far as radium is allowed to come into relationship to devitalized skin flaps. After an experience of 98 cases, Trout and Peterson state that there has been no interference with the healing of the wound.

Radium alone. Various combinations of surface and interstitial radium therapy have been used, and have been examined critically by the writer elsewhere.[1] The available figures are few in number, but tabulation has been resorted to as being the only means of giving a bird's-eye view of the present position, and of offering a ready comparison with the data already submitted for the other groupings. The results will be found collected in Table V. Radium therapy can hardly be regarded as having passed beyond its early stages, and no attempt has been made to differentiate between earlier and later techniques. The averages of Table V have nevertheless been included in Table VI so that they may be referred to easily.

[1]Brit. J. Surg., 1935, 22: 465–474.

TABLE IB.—SURGERY ALONE

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Trout and Peterson	1909–1920							22	
Harrington	1910–1927								
a. No glands		80.2				67.4			
b. Glands involved			31.7				25.7		
	1915–1923								
a. No glands		79				70.6			
b. Glands involved			37.9				22.9		
Perthes	1920			38.5				27.7	
Greenough and Simmons	1921								
a. No glands						71			
b. Glands slightly enlarged							33		
c. Glands markedly enlarged (average cases)							10		
Sistrunk	1921								
a. With glands			36.6				21.9		
b. Without glands		75.6				65.1			
c. Total cases				51.8				39	
Wiesman	1921								
a. All cases				30.5					
b. Group 1		62.5							
c. Group 2			38.5						
d. Group 3					7.1				
Bunts	1922			27.6				23.8	
Gage and Adams	1922			27					
Peck and White	1922								
a. Without axillary metastasis						65			
b. With axillary metastasis							23		
c. Total								39	
Haggard and Douglass	1923							45.7	
Walther	1923			32					
Lane-Claypon	1924								
a. Class 1		64.2							
b. Class 2			31.9						
c. Class 3			9.9						
d. Total with "complete" operation				43.2					
Lee and Cornell	1924							15	
Lehmann	1924			32				28	
Holfelder	1925			32.5				25	
Anschuetz and Hellmann	1926								
Group 1		100				100			
Groups 2a and 2b			50				40.2		
Group 2c			24.1				13.7		
Group 3					25				12.5
Total				44.8				35.3	
Braine and Massie	1926			50				27.3	
Dahl-Iversen	1927			33					
Meier	1927							12	
Schoute and Orbaan	1927			42.3				35.9	
Bucholz	1928			24				22.3	
Ducuing	1928			23.6				8.1	
Harrington	1928								
a. Glands not involved		79				70.5			
b. Glands involved			37.8				22.8		
Lane-Claypon	1928								
Class 1		85				78.5			
Class 2			40.7				24.7		
Class 3			35.2				21.9		
Portmann	1928			38.6				28.8	

TABLE IB.—SURGERY ALONE—Continued

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Greenough	1929							34	
Pfahler and Widmann	1929			32				31.3	
Schmitze. Group 1	1929					69.2			
Handley	1930			47					
Himmelmann and Lehmann a. Steinthal 1 b. Steinthal 2 c. Steinthal 3 d. Total	1930	73.5	34.7	42.5	7.1	66.6	25	34.6	7.7
Pfahler and Parry a. Glands not involved b. Glands involved	1930	75	30			77	20		
Westermark, quoting for a. Dahlgren b. Neander c. Mystrom	1930							15 16.8 21.5	
Keynes	1930–1931			45.2				37	
Gobell and Magens Group 1 Group 2 Group 3 Group 4 Total	1931	100	67.4 42.8	60.1	25	100	53.5 28	46.6	8.3
Hintze	1931							28.4	
Stubenbord	1931							9	
Wintz a. Steinthal 1 b. Steinthal 2 c. Steinthal 3	1931	75	28		7				
Adair	1932							10	
Danis	1932			59				51	
Hintz	1932							34	
Klingenstein a. Without glands b. With glands c. Total	1932					40	17	23	
Mathews No axillary involvement	1932					64.4			
Pfahler a. Without glands b. With glands	1932	75	32			80	24.5		
Taylor a. Without axillary involvement b. All radical operations	1932					70		30	
Gask	1933							36	
Pearce Gould a. Stage 1—no glands b. Stage 2—glands c. All cases	1933	65.9	39.4	48.3		57.4	22.1	33.1	
Averages		77.9	36.0	39.4	14.2	71.3	25.0	28.1	9.5

TABLE IIA.—SURGERY PLUS X-RAYS

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Pfahler and Parry a. Pre- and postoperative X-rays. All classes b. Postoperative, no glands c. Postoperative with glands d. Postoperative, all classes	1902–1922	96	63	55 59		84	55	47 49	
Schreiner a. Group 1 b. Group 2	1931					58	19		
Harrington a. Without glands b. With glands	1915–1923	80.7	42.5			66.2	26.3		
Perthes Group 1	1920	85.2							
Walther	1923			77					
Greenough	1924							24	
Lehmann Old technique	1924			55				39	
Schmitz a. Groups 1 and 2 b. Group 1 c. Group 2						64.5	42	53.2	
Averages		87.3	52.8	61.5		68.2	35.6	42.4	

TABLE IIB.—SURGERY PLUS X-RAYS

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Pfahler and Parry a. Pre- and postoperative. All classes b. Postoperative—no glands c. Postoperative with glands d. Postoperative—all classes	1922–1927	95	62	64 73		93	57	54 75	
Anschuetz and Hellmann a. Group 1 b. Groups 2a and 2b c. Group 2c d. Group 3 e. Total	1926	100	71.7 36.1	60.4	27.2	100	56.5 16.1	44.4	9.5
Braine and Massie	1926			66				31	
Meier	1927							23.5	
Schoute and Orbaan	1927			57				44.4	
Bucholz	1928			54				45.2	
Lee a. Pre- and postoperative irradiation b. Postoperative irradiation	1928							39 35	
Harrington a. Without glands b. With glands	1929	80.7	42.5			66.2	26.3		
Pfahler and Widmann	1929			58.3				43.2	
Schmitze a. Group 2 b. Group 3	1929						51.7		11.8

TABLE IIB.—SURGERY PLUS X-RAYS—Continued

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Evans and Leucutia	1930								
a. Without glands		76.5				70.6			
b. With glands			62.2				46.7		
Himmelmann and Lehmann	1930								
a. Steinthal 1		100				50			
b. Steinthal 2			25.9				18.2		
c. Steinthal 3					28.6				
d. Total				32.4				16.7	
Pfahler and Parry	1930			45.5				35	
Trout and Peterson	1930							55	
Westermark	1930								
a. Quoting Dahlgren								29.3	
b. Quoting Brattstrom								40	
c. Diathermy plus irradiation								28.6	
d. Postoperative irradiation									
Steinthal 1						60			
Steinthal 2							29.1		
Steinthal 3									0
e. Pre- and postoperative irradiation									
Steinthal 1						75			
Steinthal 2							35.5		
Steinthal 3									16.7
f. Electro-endothermy plus irradiation									
Steinthal 1						100			
Steinthal 2							42.9		
Steinthal 3									15.4
de Backer	1931			50					
Billich	1931			58.4				30.6	
Gobel and Magens	1931								
a. Group 1		100				100			
b. Group 2			64.8				52.1		
c. Group 3			41.7				33.3		
d. Group 4					0				0
e. Total				57.7				47.7	
Hintze	1931							37.9	
Lee	1931								
a. Grade A						45			
b. Grade B							24		
c. Grade C									13
Wassink	1931								
a. Without metastases		93.3							
b. With central axillary glands			65.2						
c. With peripheral axillary glands			14.8						
d. With metastases above axilla					9.5				
Adair	1932							38.2	
Hintze	1932							53	
Pfahler	1932								
a. Pre- and postoperative X-ray									
1. Without glands		65				58			
2. With glands			62				57		
b. Postoperative X-ray									
1. Without glands		96				87			
2. With glands			64				58		
c. Averaging various authors									
1. Without glands		92				74			
2. With glands			50				37		
Portmann	1932								
a. Group 1						66.6			
b. Group 2							56.3		
c. Group 3									6.2
d. All cases								42.7	
Webster	1932								
Stages 2 and 3				47				42	
Averages		89.9	51.0	55.7	16.3	74.7	41.0	40.9	9.1

TABLE IIIA.—X-RAYS ALONE

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Pfahler and Parry a. Primary operable b. Primary inoperable	1902–1922	87			42	87			30
Schreiner a. Grade 1 b. Grade 2	1914–1925					21	1.2		
Kronig a. Steinthal 1 b. Steinthal 2 c. Steinthal 3 d. Total	1920	11.8	28.1	19.5	0				
Averages		49.4	28.1	19.5	21.0	54.0	1.2		30

EVALUATION

Examination of the various figures in the foregoing tables leads to some interesting conclusions. In the first place, it is apparent that surgery *per se* is no longer unchallenged as the treatment of choice in mammary carcinoma, even in early cases without glandular adenopathy. Minor improvements in operative technique may yet take place, but broadly speaking it would appear that the resources of surgery have been exploited to their limit. That this is so, is borne out by the very slight improvement in the surgical results during the last 20 years or so.

Much discussion has taken place in recent times regarding the desirability of combining surgery with radiation. Study of the figures obtained in the course of this investigation allows of only one conclusion, namely, that the combination of X-rays with surgery offers a better chance of cure than does surgery alone. In the early cases, the advantage of this technique is not striking, but in the later cases, and when total cases are considered, the improvement in the results is seen to amount to about 20 per cent at the 3 year period, and 15 per cent at the 5 year period, an advance so great that it cannot reasonably be attributed to chance. It will be noted, and perhaps at first sight with surprise, that the very advanced cases do not appear to reap any advantage from the combined technique. To the writer it seems that the explanation lies in the damage done by encroachment with the knife upon malignant tissues.

The steady improvement in X-ray technique has been mentioned already, and is manifest in Tables IIIA and IIIB, which show the results of X-ray therapy alone. Here improvements of later upon earlier results are seen to be of the order of 40 per cent at 3 years and 20 per cent at 5 years. The 3 year figure of 94 per cent for early cases is remarkable. Wintz has stated that in the Steinthal group I it is not possible to improve upon the results of surgery, but that in Steinthal groups II and III X-radiation *per se* surpasses the best results of operation. But while the figures for X-radiation alone are few compared with those for surgery, or for the combined technique, it must be conceded that in the hands of the expert, when the technique has been evolved from large experience and is applied in a scientific manner, the results of radiation alone are seen to equal or surpass those of any other method, even in the early cases. It is impossible, however, to emphasize too strongly that such radiation results are obtained only when scientific methods prevail, and not by the random application of X-rays of unknown quality and intensity and in unknown amount.

Not least striking are the results in the very advanced cases, and it is seen that in this sphere radiation alone improves, not only upon surgery, but also upon surgery plus X-rays. This fact would appear to offer an interesting commentary upon the danger of transgressing surgically upon malignant tisues. Tissues traumatized by operative surgery

TABLE IIIB.—X-RAYS ALONE

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Pfahler and Parry a. Primary operable b. Primary inoperable	1922–1927	93			48	80			32
Wintz a. Grade 1 b. Grade 2 c. Grades 1 and 2	1925	95.2	68.2					48.5	
Wintz	1926				18.1				18.8
Lee a. X-rays b. X-rays and radium	1928							11 37	
Webster a. Stage 1 b. Stages 1 and 2	1928	100		75					
Jungling	1929				11.1				
Pfahler and Widmann a. Operable b. Inoperable	1929			83.3	47			50	23.4
Schmitze Group 4	1929								3.2
Lee Grade A	1931					55			
Wintz a. Steinthal. 1 b. Steinthal. 2 c. Steinthal. 1 and 2 d. Steinthal 3	1931	96	70	77.3	21	76	46.5	55.4	10
Adair	1932							24.2	
Hintze	1932								6.1
Pfahler a. Grade 1 b. Inoperable {1 {2	1932	88			35 39	82			25 30
Webster Operable and borderline	1932							70	
Averages		94.4	69.1	78.5	31.3	73.3	46.5	42.3	18.6

are unable to tolerate a dose of radiation as large as can be applied to undamaged tissues, and therefore the risk is real that when malignant tissues are opened up by the knife it may no longer be possible to deliver a lethal dose of X-ray therapy to any residue of malignant tissue. The same consideration undoubtedly arises also in relation to surgery plus radium.

Radium therapy alone presents an encouraging record, and further improvements are to be looked for as technical difficulties are overcome. At the present time, however, it does not quite produce the results achieved by other methods. Figures for radium beam therapy in relation to breast cancer do not appear to be available as yet, and expression of any opinion upon this matter would be premature.

Statistics are scanty regarding radium combined with surgery. There is no justification for suggesting that this is the ideal method for dealing with carcinoma of the breast. Nevertheless the results of Handley and of Trout and Peterson are interesting, as being a practical justification of a logical procedure. In the writer's opinion, however, none of the methods usually employed explores the full possibilities of the combination. Such a technique should achieve its maximum benefit in those cases which are surgically operable. The average percentage of 5 year surgical

TABLE IV.—SURGERY PLUS RADIUM

	Author	Year of publication	Percentage cure 3 years	Percentage cure 5 years
Surgery alone	Handley	1930	47	
	Trout and Peterson	1930		22
Surgery plus radium	Handley	1930	56.5	
	Trout and Peterson	1030		30

TABLE V.—RADIUM ALONE

Author and published groupings	Year of publication or period of investigation	Percentage cure 3 years or more				Percentage cure 5 years or more			
		Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Kronig (Quoted by Schmitz)	1924								
Group 1						21.4			
Group 2							16.6		
Group 3									11
Webster	1932								
Operable and borderline						60			
Keynes	1932								
Class 1		77.7							
Class 2			36.3						
Class 3			46.1						
Keynes	1933								
Operable						60			
Inoperable									28
Raven and Hare (Nat. Radium Comm. Report)	1935								
Stage 1		64							
Stage 2			30.9						
Stage 3			24.9						
Averages		70.9	36.8			47.1	16.6		19.5

TABLE VI.—COMPARATIVE AVERAGES

	Percentage cure 3 years or more				Percentage cure 5 years or more			
	Early	Late	Total or unclassified	Very advanced	Early	Late	Total or unclassified	Very advanced
Surgery alone after 1920 46 Kepat.	77.9	36.0	39.4	14.2	71.3	35.0	28.1	9.5
Surgery plus X-rays 1925 26 "	89.9	51.0	55.7	16.3	74.7	41.0	40.9	9.1
Radium alone 1924 5 "	70.9	36.8			47.1	16.6		19.5
X-rays alone 1925 14 "	94.4	69.1	78.5	31.3	73.3	46.5	42.3	18.6

Note also: Surgery plus radium (two authors only):
Percentage cure 3 years—56.5
Percentage cure 5 years—30

cures has been shown to be just under 30. A proportion of the remaining 70 per cent is lost on account of unsuspected or invisible deposits beyond the limits of surgical dissection. It is this proportion which ought to be saved in part by the utilization of the surgical access for the introduction of radium into the areas in question. In other words, radium should be used to extend the scope of the radical operation, and not in the hope of compensating the deficiencies of surgical procedures otherwise faulty.

It is evident that, when confronted with a case of cancer of the breast, a considerable array of possible lines of attack lies before the medical man, and it is not surprising that he should feel at times a considerable weight of responsibility in selecting that which will most fully serve the best interests of his patient. The work embodied in the foregoing pages has involved careful sifting of a large mass of literature pertaining to this problem, and it is hoped that it will serve a useful purpose in lessening the burden of the choice by presenting some concrete facts material to the decision. In addition, the writer hopes that the findings may be of some scientific importance at an interesting period in the history of radiation therapy.

SUMMARY

The author presents a statistical survey of British, European, and American literature, dealing with the treatment of mammary carcinoma. The numerous published classifications have been arbitrarily arranged for comparison into early, late, total, and very advanced. From a study of the literature and of the figures obtained the following conclusions are reached:

1. Surgery is no longer unchallenged as the treatment of choice.

2. Radiation combined with surgery produces results better than those of surgery alone.

3. X-ray therapy, when scientifically employed, has been shown to produce results which surpass those of any other procedure.

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THE HEALING PROCESS IN TUBERCULOUS SPONDYLITIS

A Histopathological Case Study

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INTRODUCTION

A CASE of extensive tuberculosis of the spine, which healed under conservative treatment only, provided material for instructive pathological studies. Destructive bone changes combined with osteoporosis, so common in the active stages of tuberculosis, are absent here. In this case, which was of many years' duration, the bone tissue went on to healing, so that osteosclerosis developed at the sites of skeletal lesion; in one place complete union by bony fusion occurred between two vertebræ. In an era when surgery in tuberculosis is on the rise, knowledge of two factors may be of value: first, healing may occur without surgical intervention; second, in cases of bone infection, sclerosis as seen in the roentgenogram does not necessarily mean the healing of a simple osteomyelitis, but may indicate the healing of an old tuberculous lesion.

The tuberculous disease of the spine in this study had been existent in a quiescent stage, for many years. No signs of activity were evident even at the time of death, which resulted from a marked exacerbation of pulmonary disease and a miliary dissemination of the tuberculosis shortly before the end. Healing was indicated by many tissue changes, such as fibrosis of bone marrow, osteosclerosis, bony fusion, sequestration of necrotic bone, organization of tuberculous abscesses, and scarring of diseased intervertebral discs.

Furthermore, healing was associated with evidence of immunity of bone tissue to tuberculosis, a fact substantiated by histopathological findings. Bone tuberculosis and immunity in tuberculosis have been studied extensively, yet very little information is available which correlates these investigations and develops the idea of bone immunity to tuberculosis. Randerath quotes Askanazy in regard to fibrosis of bone marrow in tuberculosis and presents his own material, but his descriptions are too morphological. In this article the pathological findings are interpreted in the light of the biological and immunological processes.

In addition, several interesting observations were made in the routine microscopical examinations of sections representing the eight vertebral segments which were involved in this case. These findings are included in this report under the separate heading of special studies.

CLINICAL DATA[1]

On examination of the patient when he was 32 years of age, a diagnosis of pleurisy with effusion and right lumbar gravitational abscess was made. During the next 3 years other abscesses formed about the right hip and sacral region, as well as in the dorsolumbar region, where a kyphoscoliosis had developed with a gibbosity at the eleventh and twelfth dorsal vertebræ. Drainage of abscesses and dietary regimen resulted in such marked improvement that the patient was sent home (about 6 years after time of first examination). He returned 1½ years later with marked aggravation of the pulmonary symptoms. Several days later his temperature rose to 102.2 degrees Fahrenheit and he developed opisthotonus, a positive Kernig's sign, and cramps in the right arm. Six days after the last admittance he became comatose and died.

The autopsy findings showed chronic pulmonary tuberculosis with advanced involvement of all lobes. There were tuberculous ulcers of the trachea, larynx, hypopharynx, and epiglottis. Solitary ulcers were found in the large bowel and lower ileum and miliary tubercles in the kidneys, spleen, and liver. The right heart was hypertrophied. The meninges were found to be free.

Examination of the spine revealed Pott's disease extending from the eighth dorsal to the third lumbar vertebra; healing had occurred with eburnation and gibbus formation at the dorsolumbar junction, where the first lumbar vertebra was reduced to a wedge-shaped fragment. A small sequestrum was present in front of this segment, while above it the intervertebral disc was completely destroyed. The eleventh and twelfth dorsal vertebræ were fused to each other by bony union. At this level abscesses

[1] I am indebted to Dr. Ernst Freund, Department of Orthopedic Surgery, Children's Hospital, for help in preparing this paper and for the use of pathological material from his private collection. Since submitting this manuscript Dr. Freund has become associated with the Florida Medical Center, Venice, Florida.

occurred, both in front and behind, elevating the anterior and posterior longitudinal ligaments, respectively, from the surfaces of the vertebral bodies. A right paravertebral abscess communicated with the prevertebral and postvertebral abscesses, which may have furnished the avenue by which infection traveled up and down the spine, involving the other segments. Many sinuses, which were partially obliterated, were noted over the lumbar spine and over the sacrum.

The rather constant narrowing of the intervertebral spaces gave evidence of the involvement of the intervertebral discs by early contact with tuberculous pus. The reaction of the bone tissue which was in relation to the infection at the surfaces was manifested by sclerosis of the bony trabeculæ associated with fibrosis of the bone marrow. In other places, which in most instances were more distant to the infective foci, the bone marrow was myelogenous in character and was associated with porotic bony trabeculæ (Fig. 8).

MICROSCOPICAL STUDIES

The accompanying X-ray photograph (Fig. 1) of the anatomical specimen reveals the general configuration and grosser bony changes of the diseased portion of the spine. A complete, detailed study was made of each of the eight vertebral segments, but only a representative composite picture of the material is presented herewith.

Bony trabeculæ. The structural transformation in the bony trabeculæ is secondary to changes in the bone marrow where it has reacted to the diffusion of tuberculous toxins. The existence of these toxins is inferred from the presence of prevertebral, postvertebral, and intervertebral abscesses (Fig. 2, *C*). The bone marrow close to the abscess formation, where the concentration of toxins is greatest, shows healing by fibrosis. The bony trabeculæ in these areas have healed by osteosclerosis. This picture is strikingly different from that seen in active tuberculosis when osteoporosis and bone destruction are prevalent. The bony trabeculæ, which are quite thick and dense in most places, owe their size to marked bone apposition as shown by the presence of many dark blue cement and apposition lines (Fig. 3). Whereas the cement lines may be quite irregular, often lacunar in outline, the apposition lines usually run parallel to the surface of the bony trabeculæ, indicating different periods of apposition. The trabecular surface, which is smooth in most places, may be covered by a blue line of quiescence. In this stage there is neither bone apposition nor bone resorption actually taking place. However, as soon as apposition by osteoblasts again becomes active the blue line on the surface becomes included in the trabecula: it is now an apposition line. These blue lines are of great aid in retracing the development of the pathological bone tissue, and make possible a clearer understanding of the entire pathological process.

The picture of osteosclerosis, as here presented, is a common one in regions of mechanical static stresses, where bone tissue becomes re-enforced by bone apposition under a stimulus such as weight-bearing, for example. In this case, however, the mechanical static demands are insignificant and may be ignored. By way of illustration, the bony trabeculæ in the region of the prevertebral abscess show osteosclerosis and the marrow spaces are filled with fibrous bone marrow. In a segment only a few millimeters above, however, the bony structure (where it forms one wall of the prevertebral abscess) shows marked osteoporosis. Mechanical irritation certainly cannot account for the sharp division between advanced osteosclerosis in one vertebra with the marked osteoporosis in the segment so close by. This osteosclerosis, which, therefore, must be inflammatory in nature, is similar to that seen in cases of healing simple osteomyelitis. This point is interesting because it demonstrates that a very high degree of osteosclerosis may also occur in a tuberculous lesion, when the bone marrow is stimulated to fibrosis and osteogenesis by a relatively avirulent toxin or when the marrow develops an increased resistance to the toxin. Farther away from the intervertebral space and its abscess, the bony trabeculæ become thinner and fewer in number. Their structure, nevertheless, is entirely pathological in that they still show many cement and apposition lines. However, the cement lines frequently show lacunar outline, which means that the vertebral bone tissue has undergone considerable structural transformation even at some distance from the focus of infection.

The foregoing picture makes it evident that the osteosclerosis has developed by a gradual,

prolonged process of bone transformation. In the early stages lacunar resorption of the bone tissue lead to marked osteoporosis, due partly to disuse and partly to inflammation in the areas of tuberculous lesions. As the activity of the disease subsided, new bone became apposed on the lacunar surfaces of the old porotic trabeculæ, resulting in the picture of osteosclerosis described previously.

Markedly active bone resorption is relatively rare in this case and occurs only in a few areas in which the tuberculous process is still active. So, for example, the lacunar type of bone resorption is seen along the ends of the bony trabeculæ which point toward the intervertebral space; many osteoclasts can be seen here in Howship's lacunæ. A similar picture is seen where the trabeculæ are in relation to abscesses filling in the intervertebral space. The peripheral fibrous tissue wall, derived from granulation tissue, causes irregularity of the bone tissue. This active bone resorption is partly due to mechanical irritation, especially pressure, exercised on the superficial bony trabeculæ; in greater part, it results from the irritation caused by toxic and inflammatory agents in the intervertebral pus cavity.

However, as obliteration of the abscess cavity occurs, the underlying bone tissue escapes pressure and new bone becomes apposed. This is nicely illustrated close to the patent prevertebral abscess, where the bony trabeculæ show signs of osteoclasia. However, when secondary obliteration of the abscess cavity has occurred by reattachment of the anterior longitudinal ligament to the bone surface, such signs of osteoclasia are absent. On the contrary, apposition of primitive bone tissue has taken place in thin layers, separated from each other by thin blue apposition lines. This clearly indicates that bone resorption occurred as a result of the open prevertebral abscess. In addition to the osteoclasia of bone, aforementioned, in relation to a focus of destruction, numerous areas of osteoporosis and bone resorption are seen within the vertebral bodies at some distance from a site of inflammation. The reason for the presence of these isolated areas of osteoporosis in such close proximity to areas of sclerosis (Fig. 4, *D*, *E*) is revealed by a closer study of the changes which had taken place in the bone marrow.

Bone marrow. In areas showing marked osteosclerosis of the trabeculæ, the bone marrow, almost without exception, is fibrous. This is especially true close to the intervertebral space, where hyperemic, loose, fibrous bone marrow is found quite densely infiltrated by lymphocytes. The degree of sclerosis is apparently in direct proportion to the fibrosis of the bone marrow. A somewhat similar picture of bone marrow fibrosis is seen in cases of fracture followed by pseudarthrosis, in which fibrosis develops to a limited extent to either side of the fracture space by mechanical static irritation. However, in this case inflammation and not mechanical stress is the cause of fibrosis. The presence of isolated areas of hematopoietic bone marrow (as already noted) in the midst of a prevailing fibrosis of bone marrow supports the inflammatory theory.

As the distance from the destroyed intervertebral space increases, the fat cells in the fibrous bone marrow become more numerous, especially along the endosteal surfaces of the bony trabeculæ. All these fat cells are in a very advanced stage of atrophy and show the characteristic halo of edema. The fat cell itself is very small, usually reduced to the signet ring form. After disappearance of its fat content, the cell protoplasm may stain dark red; the nucleus is found centrally or peripherally. This is a common picture of simple atrophy of fatty bone marrow. In this case it is complicated by the disappearance of the hematopoietic elements and the presence of considerable fibrin. This picture represents a transitional stage between the fibrous bone marrow close to the intervertebral space and the myelogenous bone marrow in the remote corners of the vertebral body (Fig. 4, *C*).

The method of transition can be followed histologically at the periphery of the area of fibrous bone marrow. In the first stage, a very marked hyperemia exists, so that the entire capillary network of the bone marrow is heavily filled with blood. Next, a very rapid disappearance of the hematopoietic elements of the bone marrow ensues, resulting from the strong

deleterious effect of the toxins on the specific bone marrow cells. As the specific elements fade, the fatty bone marrow cells, which are normally more or less hidden by the myelogenous tissue, come into sudden prominence (Fig. 5, *B*). Although the fat cells seem to resist the infection better than the specific elements, they ultimately undergo atrophic changes with the characteristic halo of edema (Fig. 5, *C*).

This atrophy of the fat cells must be considered as a result of toxic damage and not as a simple marantic atrophy due to the general cachexia of the patient. If cachexia were the basis for the atrophy, all fat cells would be expected to suffer equally. However, the fat cells in the areas of hematopoietic bone marrow are found to be perfectly normal in size and show no halos of edema. Consequently, the local toxic damaging substances, and not the patient's constitutional debility, must be blamed for the fat cell atrophy. In the final stage, which follows soon, fibrosis develops and collagenous fibers spread between the fat cells, giving the characteristic picture of *Geruestmark*, which gradually, but progressively, changes into fibrous bone marrow.

To recapitulate: The bone marrow reacts to the stimulation of tuberculous toxins in direct proportion to their concentration. Close to the focus of bone destruction, where the concentration of toxins is greatest, the bone marrow responds by marked fibrosis and osteogenesis. The toxins become more dilute as they diffuse into the bone tissue for some distance and the bone marrow reaction is less marked: atrophic fatty bone marrow with moderate fibrosis and osteosclerosis results. In the parts farthest removed from the focus of toxin production the damaging substances are most dilute or entirely absent: here normal hematopoietic bone marrow still persists and the bony trabeculæ are thin and porotic. In brief, the degree of fibrosis of the bone marrow is the index of the extent and intensity with which the toxins have invaded the bone tissues (Fig. 8).

Refutation of pyogenic cause of osteosclerosis. The objection may be raised, not unreasonably, that factors other than tuberculosis may be responsible for the development of osteosclerosis. The mechanical factor has already been discussed; there still remains the consideration of pyogenic infection, in the sense of the simple form of osteomyelitis, as a basis of osteogenesis.

Any case of tuberculosis with an open sinus is likely to become superinfected from without, and impose a secondary, non-specific osteomyelitis upon a tuberculous lesion. Theoretically, a hematogenous infection of a tuberculous abscess is also possible. By way of illustration, the fused eleventh and twelfth dorsal vertebræ show marked osteosclerosis and bony union (Figs. 1 and 11) which could be considered as the result of an osteomyelitic process rather than a tuberculous one. The considerable osteosclerosis and bone marrow fibrosis, which is so commonly found in healing osteomyelitis, is also found here, and in this manner favors the diagnosis of simple osteomyelitis.

However, in none of the tissues examined was an active pyogenic infection suggested by signs of acute inflammation and pus cells. Even the abscess cavities present are filled with exudate typical of tuberculous pus. Tubercles are present in the abscess wall, but they are rather few in number. Furthermore, as Erdheim has shown, uncomplicated tuberculous osteitis is capable of producing marked osteosclerosis. Erdheim introduced the term "para-tuberculous osteosclerosis" for this entity which he studied in the skull bone, and which is especially well illustrated in cases of tuberculous osteitis of the os calcis without sinus or abscess formation. This evidence substantially supports the view that fibrosis and osteosclerosis in this case are due to tuberculosis and not to pyogenic infection.

BONE IMMUNITY

Miliary tubercles. Bone tuberculosis in the healing stage, as studied in this case, furnishes histopathological evidence that bone tissue may acquire immunity to tuberculosis. Microscopically, the preparations reveal a great number of young miliary tubercles, consisting of a few epithelioid cells, but without any giant cells or lymphocytes. These tubercles represent a recent dissemination and correspond clinically to the terminal infection

which probably originated from the active pulmonary lesions and had no direct relation to the old tuberculous process in the spine. Most of the young tubercles occur quite constantly in areas where normal or almost normal hematopoietic bone marrow still exists. Practically none can be seen in regions of fibrous bone marrow. Those tubercles which do appear in fibrous marrow show a tendency to conglomeration and apparently are of older age than the tubercles of the terminal shower.

The conglomerate tubercles are found anteriorly in the superficial marrow spaces which communicate with the abscess cavity. Except for these areas the fibrous bone marrow is free from active signs of tuberculosis. Conversely, the marrow spaces filled with hematopoietic bone marrow show a relatively frequent incidence of miliary tubercles, so that five or six tubercles in a low power field are not uncommon (Fig. 6).

The predilection of the miliary tubercles to the myelogenous marrow and their absence from fibrous marrow indicates a difference in the allergy of these two tissues (Fig. 7). The fibrous bone marrow apparently has developed a higher resistance to the tubercle bacillus than the hematopoietic marrow. This resistance is undoubtedly acquired by the bone marrow which has been inoculated for a long period of time by the toxins diffusing from the foci of active tuberculosis. Although bone ranks high among the tissues predisposed to infection by the tubercle bacillus, it apparently can develop a high degree of immunity to such infection if exposed to the toxins for some time.

However, it should be noted that trauma may weaken the allergic resistance of fibrous tissue. This factor is brought out in the region of the wedge-shaped first lumbar vertebra. Its eroded upper surface, exposed to the abscess cavity, shows a progressive tuberculous lesion with a relatively great number of tubercles. This can be explained by the traumatization which the fibrous bone marrow suffers as soon as it becomes denuded of protective bony layers. The trauma reduces the allergic resistance of this tissue and may abolish it entirely.

Fig. 1. Roentgenogram of the involved segments of the spine from the eighth dorsal vertebra above to the third lumbar vertebra below. There is complete bony ankylosis between the eleventh and twelfth dorsal vertebræ. The first lumbar vertebra is reduced to a wedge-shaped fragment.

Origin of toxins. The origin of the toxins—capable of stimulating bone marrow to fibrosis, osteogenesis, and immunity—is still open to conjecture. Three sources are possible: first, pyogenic superinfection; second, disintegration of diseased tissues; and third, a tuberculous toxin. The reasons for eliminating superinfection of a tuberculous lesion by a pyogenic organism have already been discussed.

Next, the origin of toxins due to destruction of tissues comes under consideration. The decay of tissues involved by an active tuberculous lesion may lead to the formation of toxins. By diffusion they invade and irritate the bone marrow of the surrounding tissues which are not directly attacked by the tubercle bacillus. Cases of aseptic necrosis are analogous in so far as the necrosis of the bone marrow is certainly followed by the formation or liberation of toxins in the tissues. The surrounding living bone marrow is stimulated by the toxins to mild bone production. Thus,

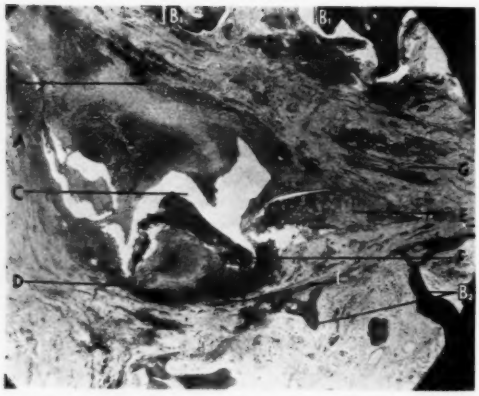

Fig. 2. The tuberculous abscess, *C*, which contains a cartilaginous, *E*, and bony sequestrum, *F*, is surrounded by granulation tissue, *D*. The abscess lies in the intervertebral space, bounded above and below by adjacent vertebral body borders, *B1-B2*; anteriorly by the anterior longitudinal ligament, *A*, and posteriorly by fibrous tissue, *G*, occupying the intervertebral space.

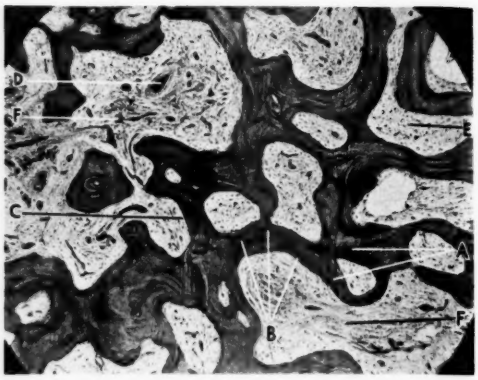

Fig. 3. The osteosclerosis of the bony trabeculæ occurs by gradual stages as indicated by the cement, *A*, and apposition, *B*, lines. Quiescence is indicated by the limiting marginal layer or *Grenzscheide*, *C*. The bone marrow is hyperemic, *D*, and shows atrophy of the fat cells, *E*, with fibrosis, *F*.

quite typically, foci of aseptic necrosis are surrounded by a zone of moderate osteosclerosis due to apposition of new bony layers on the surfaces of the old necrotic trabeculæ. However, this zone of osteosclerosis is relatively slight and never attains the marked degree observed in this case.

The third possibility is the production of toxins by the tubercle bacillus. This organism does not produce exotoxins, so the sclerosis cannot be the reaction to a vital toxic product of the bacillus. However, the tubercle bacillus does contain an endotoxin, which is well ensheathed in its wax capsule. On necrosis of the organism the toxic irritants are liberated. This concept adequately explains the source of an irritant capable of stimulating bone marrow to marked osteogenesis. This theory is therefore held to be the most feasible one.

SPECIAL STUDIES

The tuberculous abscess. The study of abscess formation in this case is interesting because of the close relationship of these areas of infection to the changes in the other tissues. The abscess cavities which extend along the anterior surface of the vertebral bodies are very narrow and are surrounded on either side by non-specific granulation tissue (Fig. 2, *D*). The anterior longitudinal ligament delineates the anterior abscess wall, while the posterior wall is formed by the eroded bony trabeculæ, whose bone marrow is condensed where the anterior bony lamellæ of the vertebræ are interrupted. The extension of the prevertebral abscess across the intervertebral space separates the annulus fibrosus of the disc from the anterior longitudinal ligament. The fibers of the ligament are quite frequently split into thinner bundles by invasion of looser connective tissue showing chronic round cell infiltration. The lymphocytes predominate, but a great number of pigment containing histiocytes are also present. They are isolated, frankly wandering, or accumulated in small groups. These cells are heavily laden with dark brown pigment, evidently hemosiderin, following resorption and organization of hemorrhage. The long duration of the process is indicated by the absence of any free hematogenous pigment in the tissue.

This picture represents an anterior superficial tuberculous spondylitis due to extension of a prevertebral abscess. The pus cavity, however, shows no signs of activity and is actually shrinking. In some places secondary fibrous tissue obliteration of the abscess occurs by reattachment of the anterior longitudinal ligament to the anterior bone surface. A few foreign body giant cells are seen in the

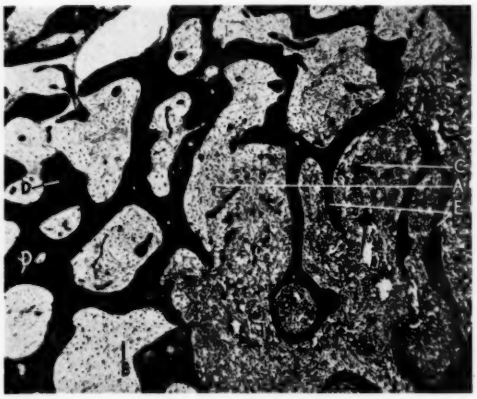

Fig. 4. At the borderline, *A*, between fatty and hematopoietic bone marrow the fat cells become more prominent. The atrophic fat cells, *B*, show the typical halo of edema. The bony trabeculæ are sclerotic, *D*, in the region of fatty and fibrous bone marrow, but are definitely porotic, *E*, in the areas of myelogenous bone marrow, *C*.

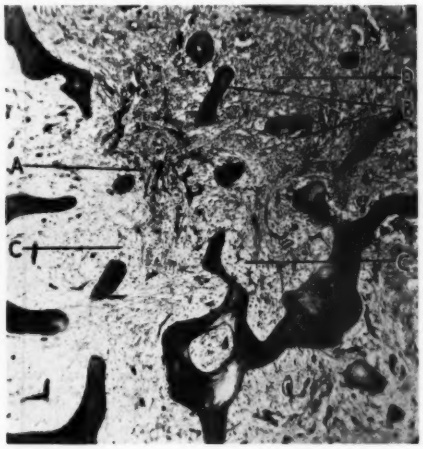

Fig. 5. The borderline, *A*, between fatty and hematopoietic bone marrow is well defined. The fat cells, *B*, become prominent as the myelogenous elements, *D*, begin to fade. The halo of edema is seen surrounding the atrophic fat cells, *C*.

granulation tissue, but no tubercles are demonstrable.

Anterior to several of the intervertebral spaces small fragments of the hyaline cartilaginous terminal layer of the intervertebral discs are found included in necrotic purulent exudate (Fig. 2, *E*). In some areas the fragments show marked lacunar outline; some are still undergoing resorption by the fibrous tissue, which also invades the abscess cavity in an attempt to organize the exudate. The hyaline cartilage, which is alive, becomes resorbed by a slow cellular process. The cartilaginous cell cavities are disrupted, but the intercellular septa of ground substance remain intact for some time.

The abscess reveals its most marked effects in the region of destruction of the first lumbar vertebra, where a small bony sequestrum lies in a large, irregular abscess cavity occupying the intervertebral space. The adjacent layer of tuberculous granulation tissue, which covers the surface of the eroded sequestrum, has free connection with the caseous material in its marrow spaces. In one place the tuberculous granulation tissue is seen invading caseous material in an attempt to resorb and organize it which suggests that tuberculous sequestra can gradually be resorbed by granulation tissue without undergoing molecular disintegration.

The tuberculous granulations show marked differences on the two surfaces of the wedge-shaped vertebra from which the sequestrum derived. The lower surface presents a picture of quiescence. The overlying fibrous tissue is compact; the bony trabeculæ, the surfaces of which are relatively smooth, show condensation and sclerosis. On the upper surface, however, the tuberculous process is progressive. The fibrous bone marrow is exposed to the intervertebral abscess cavity and has no protective fibrous tissue wall. As the fibrous bone marrow becomes denuded, it undergoes necrosis and later infection by tubercle bacilli. This area shows a large number of tubercles with giant cells; caseation develops along the irregular surface. The trabeculæ undergo extensive osteoclastic bone resorption; there are practically no signs of bone apposition present.

The posterior vertebral abscesses present many features similar to those in front; in places they elevate the posterior longitudinal ligament and force it toward the spinal canal. The posterior abscess formation, as a whole, is smaller than the anterior, but it extends farther down and at its lower end is relatively large. At the inferior aspect, the reactive changes in the marrow extend very far an-

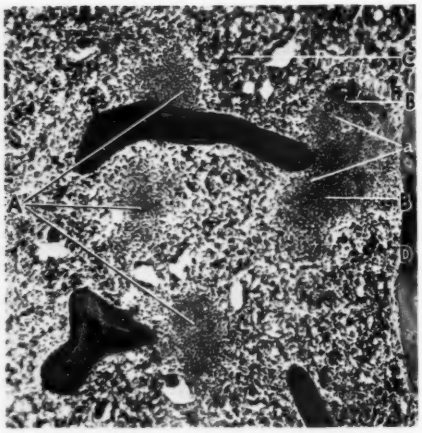

Fig. 6. Three young miliary epithelioid tubercles, *A*, are seen lying in hematopoietic bone marrow, *C*. Two other tubercles, *B*, showing a tendency to confluence, contain giant cells, *a*. On the right a portion of the terminal hyaline cartilaginous layer of the intervertebral disc, *D*, is seen.

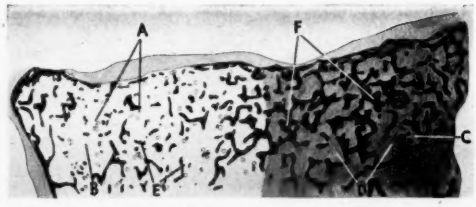

Fig. 7. This semidiagram illustrates the relative frequency of miliary tubercles, *A*, as represented by small circles, in the uncolored myelogenous bone marrow, *B*. Only a single tubercle, *C*, is seen in the shaded marrow spaces representing fibrous bone marrow, *D*. The contrast between porotic, *E*, and sclerotic, *F*, bony trabeculæ is also brought out. The photomicrograph of this section is seen (reversed) in Figure 8.

teriorly from the posterior abscess site. This signifies that at this level an accumulation of highly toxic tuberculous pus must have been present. In one place the posterior longitudinal ligament is still firmly connected to the vertebral surface, but the posterior cortex is broken down by extensive osteoclastic bone resorption. Furthermore, the bone marrow is melting down to give a typical picture of caseation. These very pronounced changes along the posterior surfaces of the vertebral bodies suggest the likelihood of spinal cord involvement, but clinically there was no evidence of cord involvement.

Although no signs of any abscesses were present on the anterior side at the same lumbar level, an old abscess cavity included in the anterior part of the intervertebral disc indicates that infection descended to this region (Figs. 8, *D*, and 9). This abscess (Fig. 9) which is filled with necrotic exudate, is surrounded superficially by a fairly smooth layer of granulation tissue still infiltrated with lymphocytes.

Fibrous tissue. Fibrous tissue plays an interesting and important rôle in the process of healing. The connective tissue filling the intervertebral space is the product of organization of the preceding abscess by granulation tissue, which is later followed by scar tissue. This is illustrated in areas in which the fibrous tissue in the intervertebral space still shows dense lymphocytic infiltration and hyperemia. Posteriorly, where the space is relatively large the fibrous tissue includes an area which is filled with fibrinous exudate which is undergoing organization by non-specific granulation tissue.

Although some of the intervertebral fibrous tissue is derived from the prevertebral and retrovertebral connective tissue, the greater part arises from the open marrow spaces of the vertebral bodies. The marrow spaces which are generally filled with a loose fibrous tissue are open toward the intervertebral space so that the connective tissue fibers of the two areas are in direct continuity with each other. The fibers which are protected by trabeculæ in the deeper bony layers are loosely joined and irregularly arranged; no static order prevails. However, we find that as the fibrous tissue fibers lose their bony protection in the region of mechanical irritation, they become more compact and assume a direction which is parallel to the surface of the intervertebral space.

The effect of mechanical irritation on the structure of fibrous tissue can be demonstrated clearly at the intervertebral surfaces of the vertebral bodies. The motion which persists between the two eroded bony surfaces subjected the fibrous tissue in the intervertebral space to pressure; a gliding component probably added tension stresses. As a result of this mechanical irritation of fibrous tissue, a

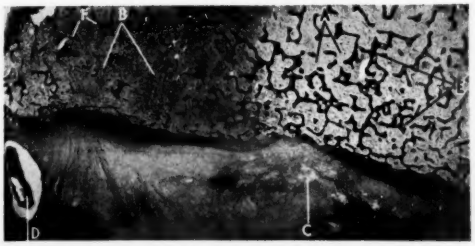

Fig. 8. The contrast between fibrous, *A*, and hematopoietic, *B*, bone marrow is nicely demonstrated. The difference between sclerotic, *E*, and porotic, *F*, bony trabeculæ is correspondingly great. Degenerative changes are seen in the intervertebral disc, *C*, which includes a healed abscess, *D*, anteriorly.

definite layer of dense connective tissue is formed at each vertebral surface. Between these two compact layers, the fibrous tissue fibers are loosely and irregularly arranged (Fig. 10). This picture imitates to a certain degree the structure of an intervertebral disc which normally has a larger central portion of loose, irregular fibrous tissue included between two more compact layers formed by hyaline cartilage. Therefore, under very marked pathological conditions the same mechanical factor, especially pressure, which helps in the destruction of the involved intervertebral disc may be the agent which makes an attempt to "re-create" a new disc from simple fibrous tissue.

Intervertebral discs. The intervertebral discs in areas in which destruction is limited show degenerative changes compatible with the age of the patient. Furthermore, this degeneration, which is not specific, is to be expected in view of the altered statics and function of the destroyed vertebral bodies. The typical changes in the discs are albumoid degeneration of the fibrous cartilage with characteristic fissuring and cyst formation. However, in one place signs of an old abscess are seen in the anterior portion of the intervertebral disc (Fig. 8, *D*), while posteriorly there are degenerative changes with small fissures, cysts, and substitution of fibrous cartilage by simple connective tissue. The terminal hyaline cartilaginous layers undergo extensive resorption from the underlying bone marrow spaces. This is a slow process without much participation of fibrous tissue or multinuclear cells.

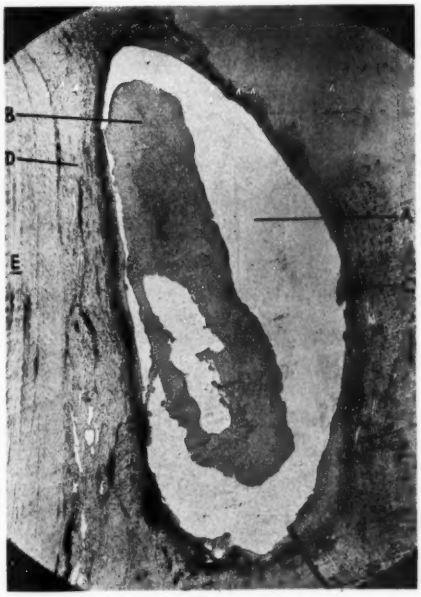

Fig. 9. The abscess cavity, *A*, contains a necrotic exudate, *B*. The abscess wall is formed by an inner smooth layer of granulation tissue, *C*, and an outer denser layer of scar tissue, *D*, still infiltrated with lymphocytes. The anterior fibrous layer of the abscess wall merges with the fibers of the anterior longitudinal ligament, *E*.

This picture, which is typical of smooth resorption by mononuclear cells, is seen frequently in cases of atrophy resulting from disuse.

The greatest amount of destruction occurs between the twelfth dorsal and first lumbar vertebræ where the intervertebral disc, including its cartilaginous terminal layers, is entirely gone. The intervertebral space is transformed into a pus cavity with walls formed by tuberculous granulation tissue undergoing necrosis in its deeper layers. However, the vertebral body has not lost much height; the inclusion of a small island of cartilage from the calcified hyaline cartilaginous layer of the disc is seen near the surface of the bone, indicating that the bone tissue has not receded materially in respect to its former relation to the disc. Although the intervertebral space immediately superior has been completely obliterated by bony fusion, a similar small inclusion of hyaline non-calcified and calcified cartilaginous tissue is seen in the spongy bone

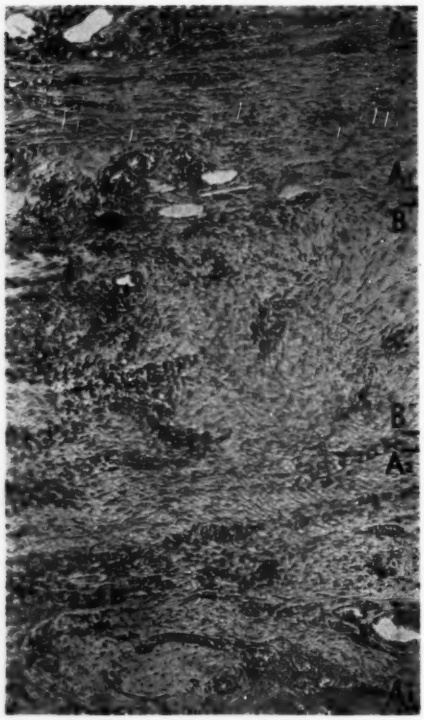

Fig. 10. The attempt at transformation of simple fibrous tissue into a primitive intervertebral disc is shown here. The upper and lower zones, *A*1-*A*2, represent dense connective tissue whose fibers run horizontally, parallel to the intervertebral surfaces of the vertebral bodies. Centrally, the fibrous tissue, *B*, is loosely constructed and irregularly arranged.

close to the posterior defect in the vertebra. These islands are portions of the hyaline cartilaginous lamellæ which survived destruction of the intervertebral disc. They serve to mark the site of the intervertebral space now obliterated by the bony fusion of the involved vertebræ.

The method by which the intervertebral disc heals after infection is shown nicely in several places. The abscess which detaches the anterior longitudinal ligament from the intervertebral disc also protrudes into a concave defect in the disc. Thus the anterior portion of the disc is formed by dense, fibrous tissue which shows a considerable number of blood vessels in its interstitial spaces. This fibrous tissue indicates that the anterior part

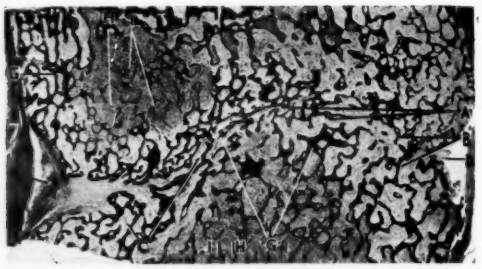

Fig. 11. This photomicrograph represents the bony fusion between the eleventh and twelfth dorsal vertebræ. The line of union is indicated by the transverse direction of the bony trabeculæ, *A*. Posteriorly the trabeculæ are assuming the new vertical direction, *B*, according to mechanic-static stresses. Fibrosis of bone marrow, *C*, is shown in relation to the line of bony fusion, the posterior defect, *D*, and the intervertebral abscess, *E*, behind the anterior longitudinal ligament, *F*. Osteosclerosis of bony trabeculæ, *G*, prevails in these areas, whereas osteoporosis, *I*, is marked in the remaining areas of hematopoietic bone marrow, *H*.

of the disc has been destroyed for a considerable distance from the anterior ligament. However, as the abscess began to shrink under organization from the periphery, the defect in the intervertebral disc also became smaller by filling up with connective tissue. In the first stages, this fibrous tissue certainly was only granulation tissue; later, it changed to denser connective tissue, rich in blood vessels. This connective tissue, therefore, represents a scarred defect in the intervertebral disc after the process of healing has progressed for some time.

Bone healing. The healing process heretofore was expressed by sclerosis of bony trabeculæ by gradual apposition of layers. Quiescence was recognized by the smooth, blue outline on the surfaces of the bony trabeculæ. Other expressions of healing are seen in the bony fusion of vertebral bodies and in the attempt to sequestrate and resorb dead bone tissue.

Bony union following tuberculous destruction is illustrated very nicely by the fusion of the eleventh and twelfth dorsal vertebræ (Fig. 11). The union is absolute, and the marrow spaces of one vertebral body communicate freely with those of the other. Nevertheless, the line of fusion is easily detected by the arrangement of the bony trabeculæ and some peculiarities of the bone marrow. The trabec-

ulæ, which are quite sclerotic in this region, are arranged in several layers parallel to the horizontal plane of the vertebral bodies. This is the method by which the occlusion of the marrow spaces along intervertebral space occurs. For some time after bony union these transverse bony lamellæ escape resorption; ultimately, however, they do become resorbed. In some places bony resorption is already more advanced, and the bony trabeculæ, which are more uniform in structure, are arranged according to mechanical static demands.

The formation of a typical tuberculous sequestrum of spongy bone is seen anterior to the wedge-shaped body of the first lumbar vertebra. The bony trabeculæ are entirely necrotic and relatively dense; their surfaces in most places are sharply lacunar. The bone marrow consists of a caseous material with partial calcification and caryorrhexis. Although the single bony trabeculæ of the sequestrum are of much greater density than those in the porotic areas of the spine, nevertheless, they are not nearly as sclerotic as those trabeculæ in the areas with fibrous bone marrow.

Furthermore, the necrotic trabeculæ show less complex structure than the sclerotic trabeculæ. This sequestrum, therefore, is evidently a portion remaining from the time when the bone tissue had not yet become so markedly porotic, and at which time osteosclerosis had not yet developed in the bone marrow. This sequestrum, no doubt, is very old, dating back to the primary tuberculous necrosis of a portion of the vertebral body when the bony structure was still of normal density. Some lacunar resorption had taken place at the surface of the bony trabeculæ as an early response to the infection, but shortly afterwards the bone marrow became caseated; thenceforth, all transforming processes stopped. At present, however, the granulation tissue which lies next to the sequestrum is seen invading the caseous marrow spaces in an attempt to resorb and organize it. This picture illustrates the fact that tuberculous sequestra may be resorbed gradually by granulation tissue without undergoing molecular deterioration.

SUMMARY

Healing, as it occurs in an old case of tuberculous spondylitis, is presented in its various manifestations. Bone marrow is stimulated to fibrosis and osteogenesis by irritating toxic substances, which are liberated by necrosis of tubercle bacilli. Fibrosis develops after the hematopoietic bone marrow loses its specific elements and after the fatty bone marrow undergoes atrophy of the fat cells. The bony trabeculæ are markedly sclerotic in the regions of fibrous bone marrow, less dense in the fatty marrow, and actually porotic in regions of normal hematopoietic bone marrow. These findings are explained thus: near a focus of destruction there is a greater concentration of toxins and therefore greater irritation of nearby bone marrow which responds by fibrosis and osteogenesis. As the distance from the point of toxin production increases, the damaging substances become more dilute and the bone tissues react to a much less marked degree. The possibility of mechanical irritation or pyogenic infection as the cause of fibrosis and sclerosis is considered insignificant in this case. Bone healing is further manifested by bony fusion of the vertebræ and by the elimination of tuberculous necrotic bone areas.

The tissues which react to toxin irritation by fibrosis also acquire an increased resistance to infection by the tubercle bacillus. Evidence to substantiate this statement is furnished by the ability of miliary tubercles to invade myelogenous bone marrow and their inability to develop in places where the marrow spaces are filled with fibrous tissue. It is assumed that the fibrous marrow, after prolonged exposure to tuberculous toxins acquired a rather high immunity to the disease. Therefore, when a miliary dissemination occurred shortly before the patient's death, the immune fibrotic areas withstood the fresh invasion and no young tubercles developed. The more remote regions, however, did not receive the benefit of inoculation with toxins; as a result the tubercle bacilli found susceptible tissue in the regions of hematopoietic bone marrow, where young tubercles are seen with relative frequency.

Although the general picture is one of quies-

cence of the tuberculous process, certain areas show activity: osteoclasia occurs in relation to abscesses and traumatization. Fibrous tissue develops in an attempt to organize abscesses and even invades the caseous tissue of a tuberculous sequestrum in an attempt to resorb and organize it. The infection in the intervertebral discs heals by fibrous tissue scarring. In some places motion persists in the intervertebral space after destruction of the disc, and by mechanical irritation tends to transform simple fibrous tissue into a primitive intervertebral disc.

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ANESTHESIA AND BLOOD LIPIDS[1]

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THE effect of anesthesia upon the concentration of blood lipids has been studied frequently in the lower animals, less frequently in man. The changes encountered among the lower animals vary from one species of animal to another, which may be shown to explain many of the apparent discrepancies in the conclusions of earlier investigators. This variation between species also exemplifies the older fallacy of assuming that changes which occur in animals likewise occur in man. In several contributions to this subject, it has been tacitly taken for granted that the demonstration of an increase in one of the blood lipids may be taken as *a priori* evidence that all of the lipids vary in the same direction. Although frequently the case, such a relationship need not always hold. In but a few cases has a complete differential lipid analysis of blood been performed before and after anesthesia due largely to the previous lack of sufficiently micro-methods for lipid estimation. Practically all of the previous work on anesthesia has been performed with whole blood. Since variations in the lipid composition of plasma are seldom the same as those in the red blood cells (7, 9, 11, 12), it follows that analysis of whole blood alone will indicate most inadequately the actual variations in blood. For these reasons it was felt that there was needed a systematic survey of *all* the lipids in *both* plasma and the red blood cells in the human subject when under the influence of anesthesia.

The earliest and one of the most thorough investigations in this field was that of Karl Reicher in 1908. Reicher demonstrated that ether, chloroform, and various other narcotics produced in dogs an increase in the *Alkohol-Aetherextrakt*, *Fett*, *Lezithin*, *Cholesterin*, and *Frei Fettsaeuren* of whole blood. These observations were subsequently confirmed in whole or in part by Bloor, Mann, Bang, Berczeller, Ducceshi, Biasini, Hospers, and Prochnow and Findeisen. Murlin and Riche stated that ether, chloretone, and morphine lowered blood fat as estimated nephelometrically, while Lattes recorded inconstant changes after chloroform anesthesia. At this point it may be noted that certain narcotic drugs have different effects which may be due in part to a time factor or to specific difference in the effect of the drug. The results recorded above have been those obtained with ether. Chloroform also causes a lipemia in dogs but it may not appear for several days, the "after rise" of Bloor. Morphine and alcohol (1, 4) and ethylene and nitrous oxide (20) apparently have little effect.

In contrast to the lipemia caused by ether anesthesia in dogs, Robinson has found that ether produces a consistent *decrease* in the cholesterol content of cat's blood.

Experiments with rabbits have uniformly shown that ether and chloroform anesthesia induce a lipemia due to an increase in cholesterol (17, 19, 20, 22), phospholipids (22) and total fatty acids (1, 22). According to Gray, paraldehyde and urethane have no consistent effect in the rabbit, but Ghose found that a fatal dose of urethane would also cause a lipemia. Bang reported that alcohol produced a marked lipemia.

Manceau has recorded a few observations on the changes in the guinea pig following chloroform narcosis, in which, curiously, he found blood cholesterol was increased but lecithin unchanged or decreased.

The conclusions of those who have investigated anesthesia in the human subject are in striking discord the one with the other. Blood cholesterol has been variously reported to be lowered (18), little changed (14), or increased (16, 25). When the total lipid alone was analysed, it was generally found to exhibit insignificant increases or no change (21, 35), but Prochnow and Findeisen (30) found that ether narcosis doubled the *Blutfette*. Von Seemen (33) recorded an initial lipemia followed by a lipopenia (for use of the term,

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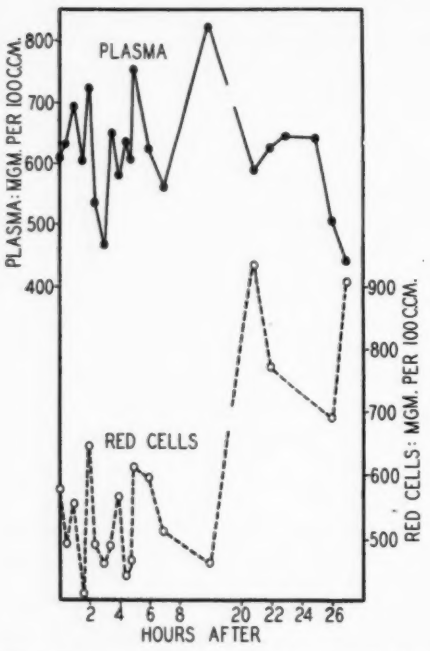

Fig. 1. The effect of anesthesia on the concentration of total lipid in plasma and the red blood cells.

lipopenia, see Boyd, 9) and later a return to normal in 13 cases. In serum the *Blutfette* has been found to be increased by Popper and Scholl (29). Blood phospholipids have received little attention but MacKay (24) demonstrated a distinct increase in inorganic phosphorus. Evipan and spinal anesthesia (16) and local anesthesia (30) have not been found to affect blood lipids in man.

METHOD

All cases studied were from the gynecological divisions of the Strong Memorial Hospital. They were selected with a view to studying only those in which an anesthetic was to be given for some time and in which the operation to be performed involved a minimum of tissue injury and hemorrhage. As most of the cases were used for class demonstrations and pelvic examinations, an anesthetic was given for at least 1 hour. Except for a few instances of major operations, the surgical interference was of a minor character such as a dilatation and curettage of the uterus. Twenty cases were studied. They received the usual pre-operative narcotic, atropine and morphine. Anesthesia was induced with nitrous oxide and oxygen and continued with ether.

Blood was taken from the arm veins before operation and again at an interval of from 1 to 27 hours after operation. The blood was oxalated and immediately centrifuged. Plasma was extracted and analyzed by Bloor oxidative micro-methods as modified by Boyd (5, 6, 8, 10). The red cells were first laked with a minimal amount of distilled water, then extracted with alcohol-ether and analyzed in the same manner as plasma.

RESULTS

Two samples of blood were secured from each of the 20 subjects and from each sample of blood two extracts were prepared, one of plasma and one of the red blood cells. In each extract the following lipid values were estimated: total lipid, neutral fat, total fatty acids, phospholipid fatty acids, neutral fat fatty acids, cholesterol ester fatty acids, total cholesterol, ester cholesterol, free cholesterol, and phospholipid. In most of the extracts, iodine numbers were also determined for the phospholipid fatty acids and the non-phospholipid fatty acids both in plasma and in the red cells. In all, upward of one thousand lipid values were obtained.

To prepare this information in a readily digestible form offered some difficulty. Only the essential or "key" values have been presented. From the data given in Figures 1 to 5, values for the remaining lipids as already listed may be calculated using the factors evaluated by Boyd (6). Figures 1 to 7 are offered as general anesthesia curves. The starting point of each curve represents the mean value of that particular lipid before an anesthetic was given. Subsequent points represent values obtained in individual cases at the postoperative hours indicated. To avoid overlapping of curves, separate ordinates for plasma and the red cells have been used in most instances.

Total lipid (Fig. 1). In plasma, no consistent change took place in the value of total

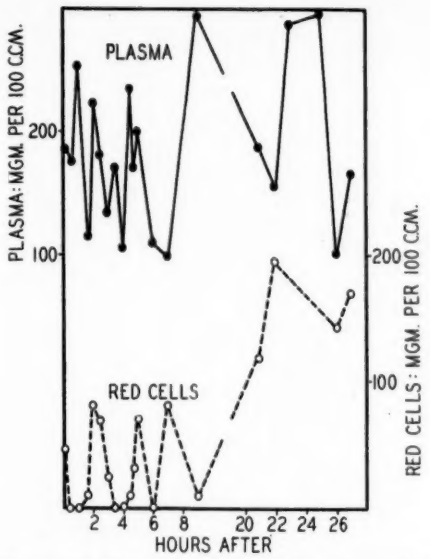

Fig. 2. The effect of anesthesia on the concentration of neutral fat in plasma and the red blood cells.

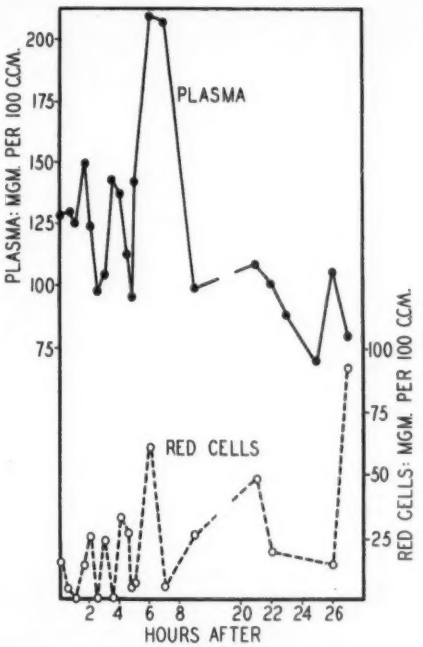

Fig. 3. The effect of anesthesia on the concentration of ester cholesterol in plasma and the red blood cells.

lipid until 24 hours had passed when there was a tendency toward decreasing values. Such occurred in 4 of 6 cases examined at about the 24 hour period. In 11 of 14 cases, total lipid was lowered in the red cells during the hours immediately following anesthesia. The next morning, however, all cases exhibited a striking increase in the lipid content of the erythrocytes.

As a net result, the lipid content of whole blood (calculated from the hematocrit readings in conjunction with the above data) decreased immediately following anesthesia, constituting a lipopenia, and increased in 24 hours or so, constituting a lipemia. The interesting feature of this lipemia of anesthesia is that it was unlike any other lipemia which, to the best of the author's knowledge, has been heretofore described. In all the known lipemias, lipids are increased both in plasma and the red cells or, more commonly, in plasma alone. The anesthetic lipemia was due to an increase in the lipid content of the red cells, an increase sufficient to offset a slight actual decrease in the plasma lipids.

Neutral fat (*Fig. 2*). Neutral fat exhibited a comparatively minor rôle in plasma. In 14 of the 20 cases, plasma neutral fat declined in value without any apparent relation to time. In the red cells, there was an early decline in the concentration of neutral fat in 10 of 14 cases and this, together with the decrease in plasma, accounted for a major portion of the early lipopenia of anesthesia. The superseding lipemia may also be seen to be due in part to a marked rise in the neutral fat of the red blood cells.

The author and H. J. Tweddell have recently found that there is a diurnal variation in the neutral fat content of the red cells (13). In this work, cellular neutral fat was found to be increased between 8 a.m. and 5 p.m. Under anesthesia, however, cellular neutral fat declined during this period since most of the operations began at 8 a.m. to 9 a.m. It cannot be gainsaid that the increase the morning after anesthesia may not have been partly due to diurnal variation. The extent of diurnal change was much less than that produced by the anesthetic. Altogether, the

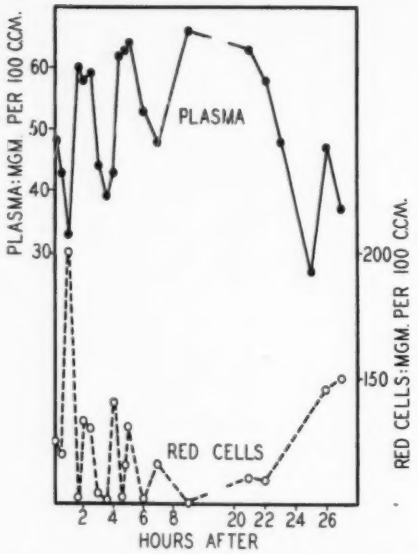

Fig. 4. The effect of anesthesia on the concentration of free cholesterol in plasma and the red blood cells.

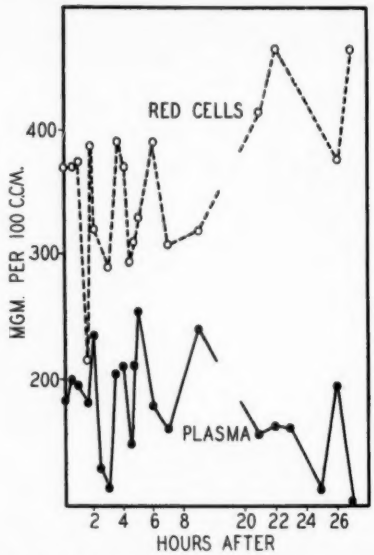

Fig. 5. The effect of anesthesia on the concentration of phospholipid in plasma and the red blood cells.

changes herein recorded for neutral fat appear to be due largely if not entirely to the effect of the anesthesia.

Ester cholesterol (*Fig. 3*). The significant change in plasma ester cholesterol occurred 24 hours after anesthesia. Immediately after the narcosis, the plasma ester cholesterol fluctuated in value but showed no uniform trends. By the next morning, all values in all cases were lower than the initial values, many markedly so. In the red blood cells, half of the cases exhibited an immediate augmentation and half an immediate diminution in the percentage of ester cholesterol. There were indications that the erythrocytes at 24 hours tended to have somewhat larger amounts of ester cholesterol, but in view of the low values and the marked variation, little significance can be attached to changes in the ester cholesterol of the red cells.

Free cholesterol (*Fig. 4*). Although plasma ester cholesterol showed no definite changes immediately after anesthesia, free cholesterol was definitely increased in 9 of 14 cases studied at this time, the change being well represented in Figure 4. From the point of view of lipid metabolism, this again is a remarkable occurrence. Of all the blood lipids, the author has invariably found free cholesterol to exhibit the least tendency to vary in health or disease (7, 9, 10, 11). Yet here is a situation in which free cholesterol changes and ester cholesterol does not. It is possible that the results may be interpreted as signifying that anesthesia has an effect on sterol metabolism apart from the rôle played by sterols and sterol esters in lipid metabolism. There were no obvious changes in the free cholesterol of the red blood cells.

Phospholipids (*Fig. 5*). The phospholipid content of plasma gave no evidence of significant changes within 9 hours of the period of anesthetic administration. By 21 to 27 hours, it tended to be lower in most cases. The phospholipid of the red cells fell in value in 10 of 14 cases immediately after anesthesia but rose to high concentrations at the later period in all cases then studied. These results were analogous to those noted for neutral fat and ester cholesterol and together with them explain the changes encountered in the total lipid curves of Figure 1.

Iodine number of the phospholipid fatty acids (*Fig. 6*). Iodine numbers of the phospholipid

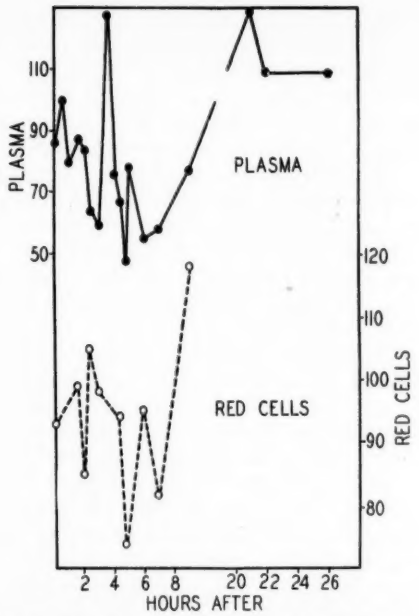

Fig. 6. The effect of anesthesia on the iodine number of the phospholipid fatty acids in plasma and the red blood cells.

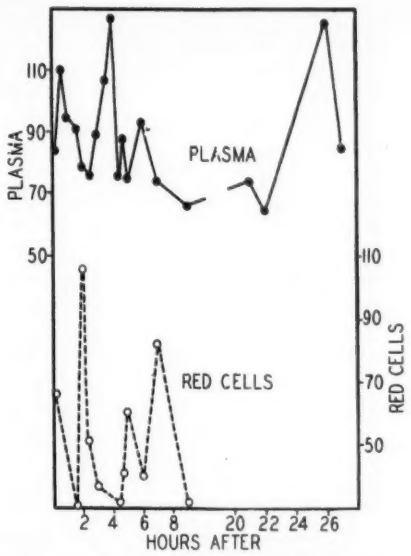

Fig. 7. The effect of anesthesia on the iodine number of the non-phospholipid fatty acids in plasma and the red blood cells.

fatty acids were determined in order to ascertain if variations in the composition of the phospholipids accompanied variations in their concentration. The phospholipids, isolated by acetone-magnesium chloride precipitation, were dissolved in hot alcohol and saponified. The fatty acids were then taken up first in hot petroleum ether and then in chloroform and their iodine number determined.

As shown in Figure 6, immediately after anesthesia the iodine number of the phospholipid fatty acids in plasma tended to decline (11 of 14 cases) while that of the red cells increased (6 of 9 cases). The results suggest that phospholipids containing the more saturated fatty acids tend to diffuse out of the red cells immediately after anesthesia, since the total phospholipid of the red cells has been shown to decrease in amount at this time. These cellular phospholipids apparently do not remain in plasma but are removed along with similar saturated phospholipids from plasma in the later 21 to 27 hour period, leaving in plasma a lowered percentage of phospholipid and that of a higher iodine number. This absorption by body tissues from plasma of relatively saturated phospholipids is of interest in view of Sinclair's postulate that such types of phospholipid (i.e. with low iodine numbers) are probably the types used in metabolism as against the high iodine number phospholipids which, according to Sinclair, are probably related chiefly to the structural make-up of cells.

Iodine number of the non-phospholipid fatty acids (*Fig.* 7). That portion of the total lipid remaining in the acetone-petroleum ether mother liquor after precipitation of the phospholipids was re-dissolved in hot alcohol, saponified, and the iodine number of the resulting non-phospholipid fatty acids determined after subtracting the iodine absorption value of the cholesterol present.

The non-phospholipid fatty acids are comprised of fatty acids derived from neutral fat and cholesterol esters. Immediately after anesthesia there has been shown to be no significant change in the amount of these lipids in plasma and, as seen in Figure 7, there was likewise no significant change in

composition as evidenced by iodine numbers. In the red cells at this time, 8 of the 10 cases exhibited a lowered iodine number which again suggests that the lipids of the red cells are taking some active part in fat metabolism at this time.

RECAPITULATION

By grouping the effect of anesthesia according to species of animal, it has been found that the results of the major portion of previous investigations may be shown to be in harmony the one with the other in spite of an apparent superficial discord. In the dog and rabbit, inhalation anesthesia produces a lipemia. The cat and the guinea pig have been insufficiently studied to warrant a final statement. Research on blood lipids during anesthesia in man has given rise to conflicting deductions but the present investigation has explained some, possibly all, of the discrepancies. It has been shown that the effect of inhalation anesthesia in the human varies at different periods after operation. And it has been shown that changes in the red blood cells differ both in nature and amount from those in plasma.

Briefly, within the first 8 to 10 hours of the postanesthetic period in the human, there occurs a lipopenia or decreased concentration of blood lipids (for use of the term, lipopenia, see Boyd, 9). This initial lipopenia was shown to be due to (a) a decrease in neutral fat of both plasma and the red cells and (b) a decrease in the phospholipid of the red cells. Some 21 to 27 hours after the anesthesia, the lipopenic period gives way to a second period characterized by a lipemia. This lipemia was shown to be due to (a) a marked increase in the neutral fat of the red cells, (b) a definite though less marked increase in the phospholipid of the red cells, and (c) a slight and more variable rise in the ester cholesterol content of the erythrocytes.

It will be noted that both the lipopenia and the lipemia owe their origin largely to changes which took place in the red cells. In fact, the lipopenic period was characterized by increasing percentages of plasma free cholesterol and the lipemic period by decreasing amounts of plasma free cholesterol, ester cholesterol, and phospholipid. The quantitative changes in the plasma lipids were opposite to those in the red cells in both periods although not involving corresponding lipids in each with the partial exception of phospholipid. The fact that the quantitative change in the red cells was greater than that in plasma enabled the red cells to be the determining factor in differentiating the periods as first lipopenic and second lipemic. As noted before, the author believes this to be the first recorded instance of a lipemia being due to increased amounts of lipids in the red cells alone.

A criticism which might possibly be applied to the results as recorded to this point is that the changes in the lipid content of the red cells might be due to changes in their volume, especially since the amount of cellular lipid has been expressed as units per volume. In reply to this, it may be noted that in practically all of the cases studied blood loss was at a minimum during operation and hence the changes recorded were undoubtedly due, for the most part if not entirely, to the effect of the anesthetic. Webster has shown that anesthesia does not produce any change in the volume of the red blood cells. While Webster's results appeared sufficiently conclusive, his general technique was applied to all of the cases herein studied and results obtained which confirmed his statements and at the same time proved that the results of the present investigation were real and not apparent.

SUMMARY

In 20 cases of minor gynecological operations the effect of nitrous oxide-ether anesthesia on the concentration of lipids in plasma and the red blood cells was determined by oxidative micro-methods.

Within the first 8 to 10 hours, a lipopenia developed due to a decrease in the neutral fat and phospholipid of the red blood cells and a fall in plasma neutral fat. This was followed by a lipemia about 24 hours after the anesthetic and the lipemia was due to a marked increase in the neutral fat, phospholipid and cholesterol esters of the red blood cells, the cholesterol fractions and phospholipid of plasma being slightly decreased in value. The unusual nature of this lipemia has been noted.

From iodine number studies, plasma was found to contain more saturated phospholipids during the lipopenia and more unsaturated phospholipids during the lipemia, the red cells discharging their saturated phospholipids in the lipopenic period. The neutral fat and cholesterol esters of the red cells became more unsaturated under the influence of anesthesia while in plasma no change occurred.

Plasma free cholesterol increased in value during the lipopenic stage while ester cholesterol did not, suggesting that anesthesia affects sterol metabolism independently of its effect through the intermediary of lipid metabolism.

The results were shown to explain many of the discrepancies in earlier studies on man, while grouping earlier data according to species served to bring into harmony certain discordant conclusions among animal studies.

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CHOLANGIOGRAPHY

A Modified Technique for the X-ray Visualization of the Bile Ducts During Operation[1]

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THE purpose of this paper is to present a method for the visualization of the biliary ducts while the patient is on the operating table and without opening the common duct.

The difficulties inherent in surgery of the biliary tract are increased by the wide variation in the clinical manifestations of common duct obstruction, the anatomical arrangement of the biliary ducts, and pathological changes which are difficult of interpretation. Consequently, the indications for choledochotomy are not usually clear except in cases presenting a typical history of common duct obstruction, and those in which at the time of operation the bile passages are definitely found to be abnormal.

In most patients with symptoms of biliary obstruction, the indications for surgical exploration of the common duct rest upon a consideration of many factors. These indications have been stated by Kehr, Eisendrath, Lahey, and others, and have been generally accepted. They are:

1. A history of jaundice accompanied by chills or fever.
2. Thickened and contracted gall bladder.
3. Thickening of the head of the pancreas.
4. Thickening and dilatation of the common duct.
5. Enlargement, induration, or cirrhosis of the liver.
6. The presence of many small stones in the gall bladder and cystic duct.
7. A cystic duct dilated by stones and separated from the common duct with difficulty, with a likelihood of spillage of the stones into the common duct.
8. The presence of muddy bile on section of the cystic duct suggestive of inflammation of the common duct.
9. The recurrence of pain or symptoms of cholangitis after operation on the biliary tract.

From the foregoing it is clear that exploration of the bile duct is performed largely on indirect evidence, the correct interpretation of which depends upon the experience and diagnostic skill of the individual surgeon. It is easy to understand, therefore, why the common duct is opened needlessly in some cases, whereas in others it is not opened when it should be. Unnecessary exploration of the common duct adds to the morbidity and increases the complications of operation, while failure to explore when disease is present renders a second operation necessary for complete relief.

Even when the common duct is opened and explored, the surgeon up to the present time has no method of making certain whether or not he has completely removed the obstruction. This not infrequently results in overlooking stones present. Under these circumstances secondary operations on the common duct, which are difficult and dangerous, become necessary.

In other cases the cause of the obstruction is not recognized, the presence of stone being assumed when stricture or tumor is present. Failure to secure the supposed stone is explained in saying that it has been pushed through the ampulla into the duodenum. The gall bladder is then removed, and when the true condition of the patient finally becomes apparent, the opportunity for sidetracking the bile may have been lost. While choledochoduodenostomy is often feasible, and transplantations of external biliary fistulas into the stomach or duodenum have been done successfully, these operations are attended with a high percentage of failures.

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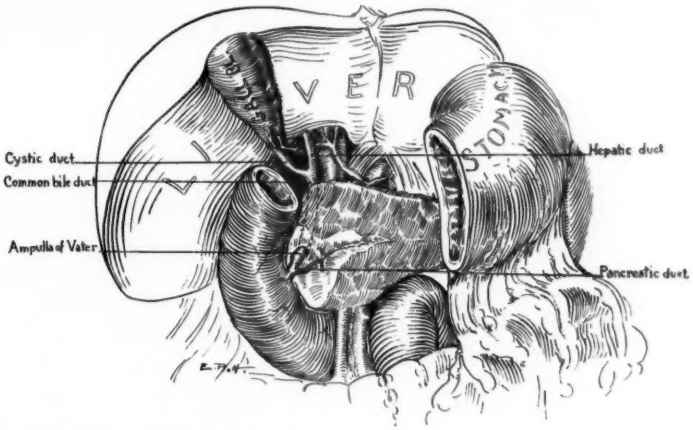

Fig. 1. Normal arrangement of biliary ducts. Note length of retroduodenal portion. In obstruction this segment of the duct is often sacculated and curved and palpation of this area is therefore difficult and unreliable.

A precise visualization of the ducts by X-ray at operation may help to obviate the unfortunate sequelæ of inadequate exploration and prevent unnecessary operation on the common duct.

In 1917 Carman reported a case of bile duct visualization after a barium meal. For a time thereafter it was hoped that a retrograde filling of the biliary tract in this manner would offer a possible means of pre-operative diagnosis of biliary tract disease. Subsequent reports, however, demonstrated that retrograde filling of the biliary tract with barium occurred infrequently and under special conditions only. In 1928 Kantor and Jaffin reviewed this subject and showed that the biliary ducts could be visualized by barium passed through the gastro-intestinal tract only when internal biliary fistulas were present, or when as a result of biliary tract disease the common duct was greatly dilated and the dilatation extended into the duodenum.

In 1927 Piccinino and Pazienzo reported the results of the injection of radiopaque substances into external biliary fistulas and were able to show that the complications of biliary tract surgery could be satisfactorily studied in this manner. In 1930 Cotte reported similar but more extensive studies. Since then contributions to this subject have been made by Overholt, Ginsburg and Benjamin, Kretchmar, and Judd. In 1932 Mirrizi made an important contribution to this subject and added a great deal to its development when he reported successful visualization of the biliary ducts while the patient was on the operating table and after the common duct had been opened. In this manner he was able to determine before the abdomen was closed whether or not the ducts had been completely freed of stones. Mirrizi injected lipiodol through a T tube inserted into the duct after it had been opened and explored. We have modified this technique by injecting the radiopaque medium into the duct before it is disturbed, and have substituted hippuran in place of lipiodol.

TECHNIQUE

A metal tunnel similar to a curved Bucky diaphragm without a grid, equipped with a sliding drawer, is placed on the operating table so that it lies under the patient's back. This tunnel is so arranged that the drawer opens on the side of the table where the assistant stands. A 14 by 17 double screen casette loaded with a 14 by 17 film is placed in the drawer. The patient is then placed on the table so that the regions of the liver and biliary passages are in the field of exposure. Anesthesia is induced, and the operative field is prepared in the usual manner. The towels

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 2. Visualization of normal biliary ducts obtained by injection of fresh cadavers. Common duct is of average size, regular in shape, and permits free flow of dye into the duodenum.

Fig. 3. Visualization of normal duct during operation. Note size and appearance of common duct as well as free flow of hippuran into duodenum (common duct not opened).

Fig. 4. Obstruction of common duct by stone. *GB*, Clamp on gall bladder. *CD*, Clamp on cystic duct. Arrow points to stones. Common duct and hepatic radicles are dilated. Small amount of dye entered duodenum. (Stones recovered when duct was opened.)

blocking the field and the skin towels for protecting the wound are stitched in place or held with aluminum clips in order to prevent metal shadows from appearing on the film. The operation is conducted as usual except that the common duct is identified before the gall bladder is disturbed. The cystic duct is then carefully dissected and clamped. By means of an ordinary 30 cubic centimeter glass syringe and a 15 to 18 gauge angulated tonsil needle 20 to 25 cubic centimeters of hippuran is then injected into the common duct. A towel is placed over the wound; the operator and assistants step aside; a portable X-ray unit is brought into position; and an exposure is made. The film is then removed and another one replaced in the drawer. The exposed film is quickly developed and the surgeon is able to view it within 6 minutes.

The operation is performed according to the indications revealed by X-ray. If the film demonstrates that the common duct is clear and unobstructed, incision and exploration of the duct can be dispensed with. If the film shows obstruction suggesting stone, stricture, or neoplasm, the duct is opened and explored, and the lesion is dealt with accordingly. After this procedure is completed, a catheter or T tube is inserted in the duct and through it 30 cubic centimeters of hippuran is injected and a second exposure is made. The surgeon is thus able to determine whether or not the obstruction is completely removed. As many exposures as seem necessary may be made. If the obstruction cannot be removed, as in the case of inoperable stricture or tumor of the duct or the pancreas, the only alternative is to anastomose the gall bladder, or common duct if possible, to the stomach or duodenum. When the surgeon is satisfied that his operation is adequate, he can close the peritoneum fully assured there will be no necessity for reoperation for an overlooked stone or stricture.

Hippuran[1] is a sterile, aqueous, 40 per cent organic iodine solution; it is a harmless substance which is excreted through the kidneys, and has proved satisfactory in every way. Various other media were tried but were given up either because of undue viscosity, high cost, or failure to produce a clear cut roentgenogram.

[1]Mallinckrodt Chemical Co. product.

Fig. 5. Obstruction (partial) of common duct by stricture. *HD*, Hepatic duct. *Cyst D*, Clamp on cystic duct. Note dilated hepatic duct and intrahepatic biliary radicles. Duodenum well filled with dye revealing patent sphincter. Common duct distal to stricture is normal.

Fig. 6. Visualization of pancreatic duct obtained by injecting common duct during operation. Arrow points to pancreatic duct. Pancreas enlarged and indurated.

Normal films for comparison were prepared by injecting fresh cadavers, dead as a result of lesions involving organs other than the liver or bile passages, and exposing films according to the same technique as used in the operating room.

RESULTS

We have used this method in 25 cases to date. In only 1 case did the first film fail to agree with the exploratory findings and check up film. In this instance the dye stopped abruptly at the ampulla and failed to enter the duodenum. Our impression was that obstruction probably existed at the ampulla, but exploration and check up films revealed the duct and ampulla patent.

In 4 instances the pancreatic ducts were visualized. It is of interest to note that in each of these 4 cases chronic pancreatitis, as evidenced by enlargement and hardening of the gland, was found on exploration. On follow-up these patients continue to complain of symptoms in whole or in part, and we believe, therefore, that this observation is of prognostic significance.

No untoward reactions have been encountered to date as a result of injecting hippuran into the bile ducts. On several occasions in obtaining check up films after operation by injecting through the drainage tube in the common duct, patients complained of transient epigastric pain radiating to the back; in 1 patient so injected on the ninth postoperative day, fever of a marked degree developed and persisted for 4 or 5 days. The fever in this instance was unexplained and may have been coincidental.

VALUE OF METHOD

This procedure is intended to furnish information not available by any other diagnostic method in present use. Since extremely small stones and so called sand bile will not show on the film, judgment as to what should be done in cases in which the evidence is not clear cut will depend as heretofore on the clinical evaluation of the case arrived at after thorough diagnostic study. For this reason, as well as for the technical difficulty associated with roentgenography and the experience necessary in the interpretation of the films, a complete study should not be omitted even if this method is to be employed.

The only contra-indication to this procedure which appears to merit consideration is

the presence of acute infection in the biliary tract. Theoretically the further dissemination of such infection appears to be a distinct possibility and it is for this reason that we have not employed this method in any such case.

Roentgen visualization of the bile ducts according to the technique described interferes in no way with the conduct of the operation. On the contrary, by providing the surgeon with visual evidence for determining whether or not the common duct should be opened, and if opened, whether or not a demonstrated obstruction has been removed, it should in our opinion be of considerable value. This is especially true in the case of common duct obstruction due to stone. With further experience, it should likewise provide valuable information in such conditions as neoplasm of the bile ducts, neoplasm of the head of the pancreas, hepatic stone, cholangitis, diverticula of the bile ducts, internal biliary fistula, and stricture.

SUMMARY AND CONCLUSIONS

1. A method for the roentgen visualization of the biliary tract during the course of operation is presented.

2. This procedure is simple; does not interfere with the conduct of the operation; is not attended by any untoward reactions; and provides valuable information obtainable through no other diagnostic method in present use.

3. Twenty-five patients have been subjected to this examination. The films in every instance except one accurately visualized the condition present as determined by operation and postoperative study. In one instance the data was equivocal.

4. In 4 cases the pancreatic duct was visualized. This occurrence, we believe, is of prognostic significance and will be dealt with in a later communication.

5. The only contra-indication to this method appears to be acute infection of the biliary tract.

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EFFECTS OF VAGOTOMY ON THE GASTRIC FUNCTIONS OF MONKEYS

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SURGICAL interruption of the nerve supply to the stomach has been frequently advocated for diverse disorders, including tabetic crises, certain "functional" disturbances, e.g., pylorospasm, and, more recently, for peptic ulcers. Reference may be made to Exner and Schwarzmann (1914), Latarjet (1922), Pauchet (1923), Gianolla (1923), Hughson (1925), Schiassi (1925), Foa (1927), Klein (1929), Winkelstein (1929), and Berg (1930). Partial gastrectomy has also been advocated as an additional measure to diminish acidity by eliminating part of the secretory epithelium (Portis and Portis, 1926), and to produce the inhibitory effects on motility which generally follow a drastic operation of this character (Hughson, 1925). Many failures are on record, such as those of Pieri and his assistants (1930) who presented a well studied series of ulcer cases in which the effects of vagotomy on gastric acidity proved to be but temporary.

Data from experimental work on animals indicate that little short of a radical resection of the whole vagal supply, preferably coupled with subtotal gastrectomy, can be relied upon to give a definite lessening of gastric secretion and acidity. Even with the combined procedure a positive result is likely to be temporary owing to potent local and humoral compensatory mechanisms.

As no detailed physiological analyses of the effects of vagotomy in subhuman primates are to be found in the experimental literature, it appeared desirable to undertake such a study, in view of the likelihood that experimentation of these higher forms would throw more light on the relevant clinical problems than the classical experiments on dogs and cats. McCrea (1926) defended denervation of the stomach for certain gastric affections and our purpose has been to analyze the rationale of such procedures along physiological lines. The present study has in fact revealed certain data having a definite bearing on gastric surgery, and we propose, therefore, to describe the experiments briefly and discuss them in detail.

METHOD OF STUDY

1. Operative procedures. During the course of previously reported experiments (27–30) on the gastric anacidity producible in the green monkey (*Cercopithecus aethiops sabaeus*, Schwarz, or *Lasiopyga callithrix*, Elliot) by parasympathomimetic drugs administered via the brain ventricles and in other ways, 10 animals were subjected to bilateral severance of the vagus nerves, the operation being performed surgically and the animals allowed to recover. In 5 cases the section was made in the neck, and in the 5 remaining it was made below the diaphragm via a midline abdominal incision. Table I summarizes the operative procedures, the complications, and the effects of the vagotomy upon (a) the motility of the cardia and (b) the secretion of acid in response to a farina gruel test meal.

2. Anatomical note. In the 10 young green monkeys of this experimental series, the right vagus divided in the lower thorax into two branches. The anterior branch formed the *anterior abdominal vagus trunk*. The posterior branch joined the left vagus to form the *posterior abdominal vagus trunk*. In one animal, not included in the present series, the left vagus bifurcated and one-half formed the anterior vagal trunk while the whole of the right vagus joined the other branch to form the posterior vagal trunk. The subdiaphragmatic approach permitted ready identification of the abdominal nerve trunks for some distance above the point at which the alimentary twigs began to be given off. In the neck, the recurrent laryngeal division usually formed a separable nerve bundle—especially on the left side—and every effort was made to spare this in the neck operations, with incomplete success, however.

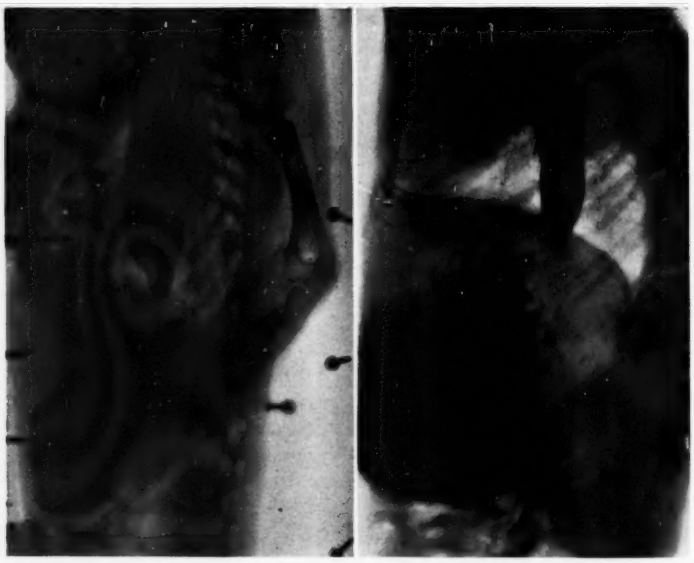

Fig. 1. Green monkey No. 8, 5 days after subdiaphragmatic vagotomy. a, left, Barium meal in esophagus (and stomach) 2 minutes after injection via rubber catheter seen in roentgenogram. Note "cardiospasm" and esophageal dilatation, with peristaltic waves. b, Residue of barium meal still in esophagus 40 minutes after injection. Note gastric atony and absence of stomach emptying.

A full account of the innervation of the stomach is given by McCrea (1926) and Kuntz (1930). Latarjet (1922) gives a valuable contribution from the viewpoint of the surgery of the human gastric nerves.

3. Postoperative complications. In accordance with the experience of earlier observers on other animals, bilateral cervical vagotomy was fraught with grave danger from pulmonary complications (Weiser, 1932, 1933). The subdiaphragmatic approach proved uniformly satisfactory as far as the general health of the animal was concerned.

Of unusual interest was the death of animal 8 on the twentieth day from a *duodenal erosion* which perforated into the pancreas, liberating bile and blood into the upper peritoneal cavity, and digesting away the posterior duodenal wall in the affected area. A small erosion on the lesser stomach curvature of animal 5 was discovered incidentally during autopsy. It was not accompanied by hemorrhage, although it extended into the muscular coat. The possibility of a postmortem or agonal change was not ruled out in this case. The mucosa of the stomach and rest of the alimentary tract were normal in all the other animals. Owing to postmortem changes, neither of the erosions described proved suitable material for histological examination.

OBSERVATIONS AND RESULTS

A. Motility disturbances. 1. Cardiospasm. In all 10 animals striking evidence of cardiospasm developed after complete vagotomy. Unilateral vagotomy in the neck caused no demonstrable effects. The lines of evidence were (1) clinical, (2) esophageal catheterization, (3) roentgenological, and (4) autopsy.

The clinical evidence consisted in the typical signs of esophageal obstruction with dysphagia, gurglings, and regurgitation of well chewed but undigested food boli. These signs were most marked in the few days after the operation but they could be demonstrated (by feeding with a banana or carrot) for many weeks, in the case of the animals which survived. The operation in the neck caused even

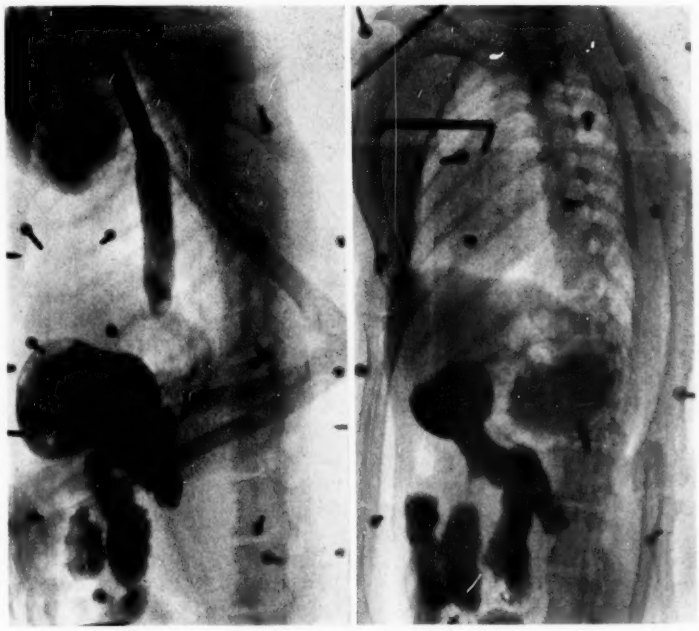

Fig. 2. Green monkey No. 13 (normal), intraventricular injection of pilocarpine (1.0 milligrams per kilogram). a, left, Two minutes after injecting barium meal. Note cardiospasm (with retention of meal in esophagus), and "mass emptying" of stomach. b, Eight minutes after giving barium meal. Note method of gastric emptying, viz., (1) fundus contracts pushing whole of meal into pyloric portion where it is retained by incisural ring, then (2) pylorus opens and antrum is emptied by a series of strong "concentric contractions" (=*mass emptying*).

more marked signs of esophageal obstruction than the subdiaphragmatic section, which suggested (a) that the disintegration of the movements of the thoracic esophagus aggravated the dysphagia, and (b) that the mere fact of operative interference around the cardia and the subsequent adhesions were insufficient to account for the obstruction. As might be expected, the local mechanism was still able to handle a more fluid intake and the dysphagia definitely improved, so that the animals which lived long enough eventually gained in weight. In view of the earlier data, it seems to us significant, however, that definite evidence of cardiospasm persisted throughout the period of observation, which in some cases was extended over many months. The passage of the stomach tube, for the purpose of conducting test meal studies, proved to be a valuable indication of cardiospasm, as the obstruction could readily be identified by means of the catheter. Further evidence was secured in a few instances by an X-ray examination following a barium meal introduced into the upper esophagus via the catheter. The typical constriction at the cardia, with dilation and vigorous peristaltic movements of the gullet, which sometimes returned the food to the mouth, were noted with the fluoroscope. The roentgenograms of animal 8, (Fig. 1, a, b) show satisfactorily the cardiospasm and long delay in esophageal emptying (Fig. 1, b) being taken 40 minutes after the introduction of the meal into the esophagus. Autopsy, especially of the animals which died soon after the vagotomy, revealed stricture at the cardio-esophageal junction and the gullet distended with undigested food. Figure 3 represents a drawing of this typical condition as encountered in animal 12.

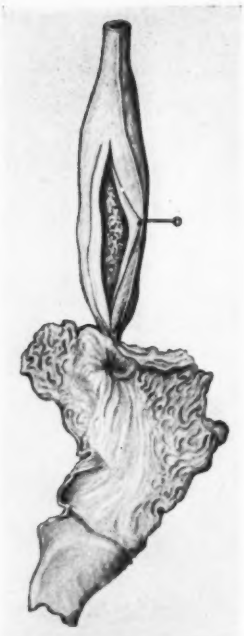

Fig. 3. Green monkey No. 12, dead of pneumonia on ninth day after completion of bilateral neck vagotomy. Drawing of stomach (opened) and distended esophagus, demonstrating cardiospasm and food retention in gullet.

2. Gastric motility. Although no planned investigation of the gastric motility had been undertaken in connection with these experiments, a number of observations have been collected which have a significant bearing upon this question. Apart from the animals with respiratory infections, all our monkeys ate ravenously after the operation and never seemed to be satisfied. It was only by means of a fluid diet and several days of fasting that the stomach could be sufficiently freed from food residues to permit of a satisfactory gastric analysis. Indeed, lavage was usually necessary prior to the giving of the test meal. The stomach was noticeably distended and relaxed in a number of the animals which came to autopsy. While a certain amount of residual food material is a common finding in normal monkeys, examined postmortem, the picture in the vagotomized animal is striking. The residues are so bulky that they tend to form a cast, as it were, of the interior of the stomach. They are free from gross fluidity and obviously represent the more solid portions of the food such as cellulose, milk-curds, etc., and the individual components of dietary articles of as much as a week previously could often be identified. Test meal samples could usually be obtained for nearly 2 hours as compared with the normal emptying time of 1 to 1½ hours. Our scanty X-ray data also afford evidence of gastric hypotonia and delayed emptying, especially "initial emptying." These findings are exemplified in the roentgenogram (Fig. 1b), and it may be emphasized that the barium meal in this case was highly viscid, and a considerable portion of it had been injected into the stomach at the commencement of the observation. The roentgenogram taken after 40 minutes and fluoroscopic observation for 10 minutes longer failed to show any onward passage of the meal into the intestines. Although we have insufficient data to specify the normal limits for the "initial emptying time" in monkeys, this animal on a previous occasion (before vagotomy), and two normal monkeys receiving the same barium meal on the present occasion, showed passage into the intestines within a few minutes. We have noted delay of 15 to 20 minutes in one or two normal cases.

3. Discussion of vagotomy in relation to gastric motility. Esophageal dysfunction, gastric atonia, and pulmonary complications were noted by Rubaschow (1912) as the result of thoracic vagotomy in 16 experimental dogs. Observations were made with the fluoroscope and also by means of a duodenal fistula.

a. Gastric emptying after vagotomy. The literature on the effects of nerve section upon gastric motility is fully summarized in the excellent review by McSwiney (1931), who cites Cannon (1906, 1911), Carlson (1913, 1922), Nieden (1921), Koennecke (1922), Watanabe (1924), Stierlin (1920), Litthauer (1919), Litchenbelt (1912), and others, for data on vagotomized dogs, cats, and rabbits. The modern viewpoint on these rather conflicting data may be summarized in McSwiney's own words (p. 493):

It is difficult to provide adequate reasons for this divergence of results. The pylorospasm and cardio-

TABLE I.—SUMMARY OF PROCEDURES CARRIED OUT ON TEN MONKEYS

Animal No.	Operation	Postoperative course	Day of death after complete vagotomy	Cause of death	Cardiospasm	Acid tide following test meal
2	One stage (neck)	Downhill	4	Pneumonia	+	No test
5	One stage (neck)	Downhill	3	Pneumonia (gastric erosion?)	+	No test
3	Two stage (neck)	Recovered	37	*Intracranial hemorrhage following intraventricular injection	+	+
11	Two stage (neck)	Slowly downhill	10	Pneumonia	+	No test
12	Two stage (neck)	Slowly downhill	9	Pneumonia	+	No test
8	Subdiaphragmatic	Recovered	20	Perforated duodenal erosion	+	+
13	Subdiaphragmatic	Recovered	170	Sacrificed	+	+
18	Subdiaphragmatic	Recovered	18	Sacrificed	+	+
22	Subdiaphragmatic	Recovered	160	Sacrificed	+	+
26	Subdiaphragmatic	Recovered	85	*Intracranial hemorrhage following intraventricular injection	+	+

*These 2 cases represent the only such accidents in over 100 intraventricular injections on 15 monkeys.

spasm described by Klee (1912–1919), Exner and Schwarzmann (1912, 1914) as immediate on vagal section are purely temporary and probably due to irritation of the nerve section. The retention is then probably due to early gastric paresis aided by reflex irritation of the remaining fibers. Some investigators may have paid too little attention to normal variations in peristalsis and emptying time, and these may be considerable. The period of postoperative examination has, in many instances, been too short, as Hughson (1925) has pointed out that any abdominal operation, even a simple laparotomy, delays the emptying of the stomach, and this effect may persist for some time. Koennecke (1922), however, who states that there is a definite delay in emptying, carried out his investigations over a period of 11 months. It appears clear, therefore that the immediate effects of vagotomy, splanchnicotomy and denervation of the stomach are similar, namely, retardation of function. After a period, the peripheral (intrinsic) nervous mechanism assumes control of the denervated stomach, and only one permanent symptom of importance, i.e., a decrease in initial emptying time, is observed.

Meek and Herrin (1934) subjected 10 dogs to bilateral thoracic vagotomy and studied them for over 5 months by means of the fluoroscope, stomach pump, and forced (apomorphine) emesis. The initial and final emptying times were carefully determined for several varieties of meal. The nature of the meal was found to be all-important. Vagotomy produced a permanent decrease in gastric "tonus" which greatly hampered the emptying of solids (including biscuit, milk curds, and precipitated barium) whereas it facilitated, especially initially, the onward passage of fluids. The accumulation of the delayed solid constituents ballooned the stomach and helped to increase the local tonus. This, coupled with a gradual postoperative hyperfunction of the peripheral mechanism, kept the animals in excellent condition. A contributory factor was the absence of satiety, due possibly to section of vagal afferents of a normal reflex that inhibits overfeeding. They noted a transient period of dysphagia due to paresis of the lower esophagus without genuine cardiospasm.

Our experience with vagotomized monkeys is seen to be in complete accord with this recent work, except with respect to cardiospasm.

b. Cardiospasm after vagotomy. Our evidence, from experiments with monkeys, clearly indicated a persistence of this phenomenon for many months after vagotomy, and may be interpreted along the following lines: Vagotomy removes the extrinsic reflex mechanism for the *co-ordination* of esophageal and gastric movements and for the control of the relaxation of the cardia. As we have repeatedly observed by catheter exploration and by X-rays, vagus stimulation by pilocarpine and large doses of acetyl-choline, causes cardiospasm (Fig. 2a) by an action, presumably, on the parasympathetic motor (efferent) endings. The locus of action is quite periph-

eral, since these drugs, in our experience, increase the cardiospasm even in the vagotomized animal. After vagotomy, the condition at the cardia is one of *achalasia* or removal of the co-ordinating reflex. The component of this reflex, which is important for the entry of food into the stomach, is the phase of relaxation. After vagus section, therefore, the cardia does not relax properly. Whether there be a true spasm in addition to the failure to relax will depend on the state of the local muscular "tonus" and doubtless this varies from time to time and animal to animal. The constancy and persistence of a true cardiospasm in monkeys suggests that this animal, in contrast to the dog and cat, has a high intrinsic tone of the cardio-esophageal musculature. The question arises: may this be correlated with the known occurrence of striated muscle fibers in the lower esophagus of monkeys (and man)? We conclude that the adaptation of the mechanism of the cardia to the interruption of its normal vagal integration depends upon the *local* motility control. The smooth muscle wall of the cardia of the cat and dog may be expected to assume a peristaltic function although in the normal animal (McSwiney, Alvarez) its contractions are "tonic" rather than "rhythmic." The monkey's cardia, rich in striped muscle, is less able to develop rhythmicity and evinces a high grade of "tonus" ("postural" contraction) after vagal section. The fluidity of the food and the size and character of the boli swallowed play a correspondingly more important rôle in the overcoming of the handicap to the feeding mechanism in these animals.

B. Secretory disturbances (gastric). 1. Acidity. In 18 examinations on the 6 vagotomized animals indicated in Table I (last column), there was never observed any diminution in the acid tide following a farina gruel test meal administered into the stomach via a tube. If anything, the acidity was rather increased after the bilateral vagotomy. Observations have been made as early as the sixth day after vagotomy. The unilateral operation was quite without demonstrable effect. The complication of food residues due to the stasis in gullet and stomach could be overcome by washing out with lukewarm water prior to the giving of the test meal, without materially influencing the results of the gastric analysis. In the animals surviving subdiaphragmatic vagotomy for long periods, a careful diet plus 36 to 48 hours' starvation proved adequate preparation for the fractional gastric analysis.

2. Mucus. Evidence of adequate mucus secretion was obtained in all gastric samples from vagotomized animals. *Bile* was rarely encountered.

3. Vagotomy and the anacidity due to (intraventricular) pilocarpine or acetyl-β-methyl choline. As reported previously (29), pilocarpine caused a complete abolition of gastric acidity (not affecting total chlorides) at the following threshold (per kilogram) doses, viz.: (1) 0.2 milligram via lateral cerebral ventricle, (2) 2.0 milligram intravenously and (3) 6.5 milligram subcutaneously. After complete subdiaphragmatic vagotomy, animal 22 failed to show the anacidity effect with intraventricular injections of pilocarpine in doses of 0.3 and 0.5 milligram per kilogram, but 1.0 and 1.5 milligrams doses gave the typical response. Animal 26, after vagotomy, showed anacidity from intraventricular pilocarpine in doses of 0.5 milligram per kilogram (two occasions). Larger doses of pilocarpine were effective in producing gastric anacidity in vagotomized monkeys, Nos. 18, 13, 8. Before vagotomy, animal 22 showed anacidity after an intraventricular injection of acetyl-β-methyl choline in a dose of 7.0 milligrams per kilogram. After the vagotomy, 8.5 milligrams per kilogram were unable to abolish the gastric acidity, but 10.0 and 12.5 milligrams succeeded. These data suggest that any raising of the intraventricular threshold for the anacidity effect noted with parasympathomimetic drugs is slight, never reaching the intravenous threshold. Vagotomy, therefore, has lent no definite support to the possibility that the low intraventricular threshold for the anacidity effect might be due to a "central action" of the drug, and we are not prepared to subscribe to this explanation until more convincing evidence be adduced.

4. Discussion on the rôle of the vagi in gastric secretion. Hartzell (1930), using dogs and carefully controlling the psychic factor, studied the (meat) test meal acidity for 6 weeks be-

fore, and 5 months after, operative vagus section. Four animals with presumably complete severance of the intrathoracic vagi developed a marked lowering of gastric acidity. One case, in which the posterior vagal trunk was missed, showed unaltered curves. Two cases of subdiaphragmatic vagotomy (probably incomplete) gave variable results. Vanzant (1931) found that 4 of Hartzell's dogs which survived bilateral vagotomy (including 3 of the intrathoracic route) ran an almost normal acidity after a year or two. Shapiro and Berg (1932, 1934) found that even shorter times (4 to 6 weeks) sufficed for recovery to an approximately normal level of the acid secretion in a Pavlov pouch and in the gastric remnant after vagotomy combined with a subtotal gastrectomy. Friedenwald and Feldman (1932), using an alcohol test meal and histamine stimulation on a series of 22 dogs, obtained little evidence of hypoacidity after a variety of partial vagotomies, but severance of the posterior (left) vagal trunk occasionally effected some hydrochloric acid lowering. Thompson (1930) found that bilateral subphrenic vagotomy lowered the gastric secretion in the pylorectomized stomach of dogs, but attributed a major rôle to the neutralizing influences of food proteins and regurgitated bile. De la Camp (1929) noticed that vagotomy did not abolish the histamine hyperacidity and tendency to peptic ulceration in experimental rats.

Hartzell (*v. supra*) reviewed the earlier literature. The importance of the rôle of the vagus nerves in the regulation of gastric acidity came to be recognized in the latter part of the 19th century. Hartzell cited Ducceschi (1917), Bircher (1920), Stierlin (1920), Borchers (1920), Latarjet (1922), Foa (1927), Dudek (1927), and Alvarez (1929) as obtaining experimental evidence (chiefly on dogs) that diminished gastric secretion could result from operative interference with the gastric vagal innervation, especially in conjunction with additional surgical procedures such as the Pavlov-Heidenhain pouch operation or partial gastrectomy.

Physiologists distinguish several phases in the normal stimulation of the gastric secretion. Pavlov (1910) discovered the initial (first phase) reflex (or psychic) secretion and believed it to be dependent upon the integrity of the vagi (the efferent path), a conclusion supported by Farrell (1928). Orbeli (1906) noted after vagotomy a marked reduction in the secretion of both acid and pepsin in Pavlov pouch dog fed *via* a gastric fistula. He concluded that the reflex secretion continued from the stimulation due to the food in the stomach, even in the absence of a psychic factor. The fact that some pouch secretion did occur in Orbeli's experiment suggested that a stimulating substance (hormone) is carried through the blood stream from the gastric remnant to the fundic pouch. Edkins' *gastrin* (1906) was a secretogogue extract of the gastric (antral) mucosa and Popielski (1909) and others showed that a number of tissues can yield similar extracts. Rasenkow (1925) recorded a stimulation of both hydrochloric acid and pepsin secretion in one dog after transfusion with the blood of another dog which had recently been fed. Lim, Ivy, and their co-workers were unsuccessful in demonstrating this in a crossed circulation experiment. Ivy and Farrell (1925) were able, however, to transplant a gastric (greater curvature) pouch into the (lactating) mammary gland. This pouch was ultimately without its old blood and nerve supply, yet it gave a typical secretion (a) when food was ingested into the gastric remnant and (b) when the pouch itself was stimulated mechanically (balloon) or chemically (food). Klein and Arnheim (1932) successfully repeated this experiment and Klein (1932) further made pouches from the mucous membrane alone, without the muscular coats and plexus of Auerbach. The same secretory powers were observed, and the high and constant level of the total chloride values were especially noted. Carlson (1919, 1923) recorded that vagotomy failed to abolish the "continuous secretion" of the *resting* pouch or fistulous stomach of dog and man.

Ivy and his co-workers have also studied a third or *intestinal phase* of gastric secretion. The evidence all points, therefore, to a certain secretory function of the vagus which plays the dominant rôle in the initial or psychic phase of secretion but, once the food

has entered the stomach, local and hormonal stimuli begin to play a more and more important part, the reflex (vagal) phenomena persisting in a subsidiary rôle.

Our own data on monkeys contribute evidence in favor of the view that the local (gastric and intestinal) phases of acid and chloride gastric secretion are well able to continue in spite of the operative severance of the vagus nerves.

GENERAL DISCUSSION

1. *Regulation of gastric acidity.* Bickel (1925) reviewed the experimental data which point to the parietal (oxyntic) cell as the unit primarily concerned with the gastric hydrochloric acid secretion. In a series of papers on the physicochemical aspects of gastric acidity, Hollander, Cowgill, and Gilman (36, 37, 41–45) gave evidence that (1) the total chlorides of the gastric juice paralleled the concentration of electrolytes in the circulating blood, and (2) the *maximum* free acidity obtainable in the pure gastric juice of dogs, cats, and humans was close to 150 milli-equivalents per liter (pH = 0.91 ± 0.02) which significantly approximated to "isotonicity" with the blood chlorides. These data indicated that the oxyntic cells secrete "all-or-nothing" to maintain the ion equilibria between the gastric contents and the blood supply. This is analogous to the rôle of the renal glomerulus in urine formation. It conceives of each acid secreting cell pouring out hydrochloric acid (or its intermediary?) to meet an osmotic requirement. It admits of individual cellular activity under (a) local control (metabolites, direct stimuli) and (b) hormonal influences acting via the blood stream, and, perhaps, (c) secretory nerve impulses, but the primary controlling mechanism is the osmotic state of the blood relative to the gastric contents. Although the classical description of the histology of the gastric mucosa emphasizes a preponderance of oxyntic cells in the fundic glands, they are by no means absent from the pyloric mucosa, as is evident from the observations of Shapiro and Berg (1934) that the total acidity in the pyloric remnant after subtotal gastrectomy was but little lower than that in a Pavlov pouch made at the time of the operation. Priestly and Mann (1932) also gave data to show that the pyloric mucosa can secrete an abundance of hydrochloric acid. Shapiro and Berg's experiments also emphasize that a very small amount of acid secreting mucosa can elaborate a large quantity of acid, the implication being that the osmotic equilibration mentioned is *complete* under nearly all conditions. Bernheim (1932) found that ligation of the gastric vessels either necrosed the stomach and killed the animal or, more usually, a collateral circulation quickly developed and permitted the continuation of a normally acid gastric secretion. Variations in blood supply would seem, therefore, not to exert an appreciable influence on the attainment of the osmotic equilibrium. Although these deductions are tentative, it would seem clear that the acidity is very difficult to influence by experimental procedures aimed at its fundamental mechanism. There is no evidence to implicate the vasomotor nerves as a direct factor in the control of gastric acidity. Vascular involvement in conditions of disturbed motility (e.g., spasm) is a hypothetical and unlikely contingency. The only established facts to date are that the gastric mucosa can secrete acid provided it has a blood supply, and all conditions effective in stimulating gastric secretion involve an increased blood supply (Lim, Ivy, and McCarthy). A direct secretogogue action of the vagi upon the acid secreting cells would seem likely from the occurrence of acidity in the gastric juice from a Pavlov but not from an Heidenhain (denervated) pouch in response to psychic stimuli (Pavlov, Ivy). It is quite certain, however, that the vagi are not an essential pathway for the secretory impulse since the vagotomized stomach or pouch secretes acid in response to histamine and local mechanical and chemical stimuli (*v. supra*). The data thus tend to minimize the importance of vagal influences on the acid secretion and point to the circulation as the immediate controlling factor. Perhaps some light may be shed upon the question by the study of the parallelism of histamine acidity and intragastric (or pouch) temperatures, used as an index of the circulatory activity by Thiessen and Snell (1933).

On the other hand, there is abundant evi-

dence that the "organic" secretions of the gastric mucosa are under the regulating influence of nervous factors, both excitatory and inhibitory (Pavlov, Babkin). We may refer particularly to the data secured by Babkin and his collaborators on the composition of the gastric juice from canine pouches under various experimental conditions. Babkin and Komarov (1932) have stressed the importance of the *mucus* secretion. In addition to "visible mucus" (from the surface epithelium) there is "dissolved mucus" which is secreted, in all probability (Babkin, Webster, Komarov), along with the pepsin from the "chief" cells of the gastric glands. Mucus (free and dissolved) is able to neutralize a considerable degree of free acidity in the stomach, especially at the beginning and end of the secretory period; it also possesses antipeptic powers. Babkin found that the composition of "mixed gastric juice" depended upon the type of stimulation by which it was called forth. Thus (a) sham feeding (involving vagal stimulation) and (b) pilocarpine injections (small doses, subcutaneously) result in a juice which is rich not only in acid but also in pepsin and mucus, while (c) true feeding and, especially, (d) histamine injections give a highly acid juice poorer in organic constituents. Two experimental complications must be ruled out, viz., (1) an irritant factor associated with inflammatory products from the mouth of the pouch or with the sampling apparatus, and (2) reflex factors associated with the peritoneal and other injury during the period of a few weeks after the pouch operation (ref. Shapiro and Berg). After elimination of these technical difficulties, there remains good evidence that the organic part of the gastric juice is secreted as an alkaline, chloride-rich material best exemplified in the small volume of "continuous secretion" obtainable in the "resting phase" of the pouch.

If a major rôle (Babkin) in the neutralization of the acidity of the parietal cell secretion can be ascribed to the alkalinizing effects of the organic secretions of the principal and mucoid cells, it is easy to explain any variation in the acid values of the "mixed juice," even from a gastric pouch where casual factors such as swallowed saliva, food, and regurgitated bile (Boldyreff, 12) may be completely ruled out. Our data on monkeys are not free from the complications of these "casual factors" but, in an analysis, do afford evidence that the gastric neutralization mechanism can be extremely effective in these animals under certain experimental conditions. Thus, pilocarpine (29) and acetyl-β-methyl choline (30) can produce a complete anacidity in from 5 to 10 minutes when given in sufficient dosage *via* intraventricular, intravenous, or subcutaneous routes. The inability of vagotomy to alter significantly the intraventricular threshold for this effect, is interpreted as strong evidence against the entertaining possibility of a "central action." An alternative explanation, based on theoretical considerations, is tentatively advanced as follows: Presuming the anacidity to result from a gastric neutralization mechanism (*v. supra*), it will require a *continuous* secretion of sufficient alkalinizing material throughout the digestive period. *Subcutaneous* administration of parasympathomimetic drugs, directly stimulating the chief and mucoid cells, would require the largest dosage owing to the slow rate of absorption *via* this route. *Intravenous* injection would be expected to get the drug to the peripheral locus (the gland cell) most quickly, but the rapidity of elimination and inactivation of the circulating poison would militate against a sufficiently prolonged action to be really effective. The temporary effect of intravenous injections of acetyl-β-methyl choline was especially noted (Ferguson and Smith, op. cit.), although it was not strictly confined to this route of administration. *Intraventricular* injection might be supposed to have the advantage of a moderately rapid absorption rate coupled with a *continuous absorption* over a long period[1] thus maintaining the effective neutralization of gastric acidity by the "organic secretion," with the minimum dosage. An analogy is seen in the superiority of the intraperitoneal route for continuous absorption of glucose saline, and the barbiturate anesthetics, etc. The antagonizing action of atropine (again a

[1]The literature yields insufficient information as to the rate of absorption of dissolved substances *from* the cerebral ventricles, and we are at present engaged in a series of experiments by which we hope to throw light on this point.

peripheral action) is quite in accord with this explanation.

2. Nerve supply of stomach and ulcer formation. Much experimental work has been done on the relation of peptic ulcer to the neuro-motor and neuro-secretory mechanisms of the stomach, and a full account of the rather conflicting literature appears in the articles by Greggio (1916), McCann (1929), Cushing (1932), and Best and Orator (1932). The rabbit has usually been employed, which is unfortunate as this animal may show gastric lesions after a wide variety of experimental procedures; and because it is prone to serious sequelæ from vagotomy or splanchnicotomy (Alvarez, 1929). Dogs were used by Latzel (1913) in a series which included 10 cases of hemorrhagic erosions and ulcerations following subdiaphragmatic vagotomy. The following conclusions may be drawn from a survey of the literature: (1) hemorrhagic lesions and acute erosions (sometimes perforating) are much easier to produce than true (chronic) peptic ulcers, indicating that the underlying pathology is far from simple but must embrace a number of varying factors; (2) vagotomy (bilateral) is likely to be followed by such lesions, but splanchnicotomy and also adrenalectomy (72, 91) are probably even more effective in producing erosions; the incidence of lesions varies greatly in the different records; (3) irritation of the vagi may be a factor (Singer, 1928; Stahnke, 1924; Keppich, 1921; Lorenzi, 1916; dalla Vedova, 1900; *et al.*); (4) Okkels' (1927) suggestion that pathological changes in the vagus nerves, or in the vagal nuclei (Singer, 1928), may dispose to ulcer chronicity is not supported by experimental evidence (Best and Orator, 1932).

While the extent to which the central nervous system is implicated in the ulcer problem (McCann, 1929; Cushing, 1932) is beyond the scope of the present discussion, it may be noted that the experience of Fulton and associates in the Yale laboratory suggests a significant incidence of alimentary lesions in monkeys with experimental injury to the hypothalamus, confirming Cushing's human data and those of Keller (1933) on dogs.

No discussion of the pharmacological approach (Westphal, 1913; Friedman, 1918; Underhill and Freiheit, 1928; Light, Bishop, and Kendall, 1932) will be attempted beyond noting that we have given 15 monkeys over a hundred intraventricular injections of pilocarpine in doses from 0.15 to 17.1 milligrams per kilogram without the slightest evidence of gastric or intestinal lesions that could be related to these injections. We have, on occasion, even administered dilute hydrochloric acid to counteract the anacidity noted in these experiments. One animal, only, showed a small peptic ulcer on the lesser curvature at the end of one of several linear abrasions caused by the previous passage of a hard stomach tube. In life this animal showed hyperacidity barely affected by massive doses of pilocarpine (29).

3. Applications to the surgery of peptic ulcer. Clinical experience has amply demonstrated the need for control of the gastric acidity as an integral part of the treatment of peptic ulcer. Our experiments on monkeys show that vagotomy may be followed by gastric lesions (albeit rarely). The procedure is ineffective in controlling the gastric acidity of these animals. Our earlier data proved the ability of parasympathomimetic drugs, suitably administered, to abolish the normal gastric acidity, although failure was recorded with one case that developed a traumatic ulcer. Apart from the strong condemnation of these drugs on account of their unpleasant side-reactions, they would not be suggested for clinical use in the light of the previous discussion. Vagotomy and subtotal gastrectomy, proved unreliable, are also to be censured for the same scientific reasons. "Actual" gastric acidity represents the admixture of the hydrochloric acid secretion of the parietal cells with the alkalinizing secretions of mucus and pepsin. Experimental attempts to abolish acidity by lessening acid secretion are bound to fail, because the oxyntic cells, if they function at all, will secrete maximally (as determined by simple osmotic considerations) and their activity is not modifiable by nerve section, mucosal removal, and vascular changes. The practical control of gastric acidity is, therefore, largely a matter of simple neutralization. With vagotomy and gastrectomy, complicated neutralizing factors may be in-

troduced: (1) disturbed balance of secretions, (2) unexplained postoperative hypo-acidity, (3) alkalinizing inflammatory materials in stomach remnant (postoperative), (4) regurgitation of bile (largely discredited).

In conclusion, therefore, it may be argued that, in so far as they aim to modify gastric acidity and motility and so alleviate the symptoms rather than strike at the cause (still, regrettably obscure) of ulcer, surgical procedures are open to the criticism that they interfere more or less seriously with the normal physiological functions of the stomach. Both the movements of the organ and the acidity of its secretions are amenable to a certain degree of control by medical measures such as rest, diet, alkalies, "mucin" (Brown, *et al.*), drugs, and so on. There are definite indications for surgical interference, e.g., hemorrhage, perforation, obstruction, or danger of neoplasm. *Gastro-enterostomy* has been proved effective in neutralizing the gastric acidity by a reflux of alkaline bile. A number of surgical details must be followed in order for this operation to achieve the purposes for which it is intended, viz., (a) relief of obstruction, (b) regurgitation of bile into the stomach. It may fail in certain cases and in others be followed by complications such as ulceration of the site of anastomosis, etc. Nevertheless, this type of operation has been much used where conservative measures have failed or where economic and occupational reasons militate against effective non-surgical treatment. It is thoroughly rational in the light of the foregoing physiological discussion. Whether the same can be said for the more radical surgery of denervation and subtotal gastrectomy (particularly in the absence of the cited "major" indications) may be discussed not only from the clinical viewpoint but also from the standpoint of the conclusions reached in the review which we have presented concerning the underlying mechanisms for the control of the stomach functions.

SUMMARY

Complete operative severance of the vagus nerves of the green monkey (in the neck, 5 cases; subdiaphragmatic, 5 cases) resulted in the following sequelæ:

1. Cardiospasm, of a persistent type, occurred in all cases; there was evidence of gastric hypotonia and of delay in the onward passage of *solid* foodstuffs.

2. The acid tide following a test meal was not lowered in the 6 animals subjected to fractional gastric analysis.

3. Only a slight rise occurred in the intraventricular threshold for the anacidity effect previously found as a typical response to injections of the parasympathomimetic drugs, pilocarpine and acetyl-β-methyl choline (hydrochlorides).

4. Two animals showed mucosal erosions at autopsy, one case in the stomach and the other in the duodenum, the latter leading to the death of the animal.

The possible rôle of the vagi in (a) peptic ulcer, (b) gastric motility, and (c) the secretion of the gastric juice, is discussed. Consideration is also given to the application of the physiological data to an evaluation of the rationale of gastric surgery.

It is a pleasure to record our thanks to Professors John F. Fulton, H. G. Barbour, and G. R. Cowgill, of Yale, and A. D. Keller, of Alabama, for their unfailing interest and helpful suggestions. The experimental work has been facilitated by a grant of the Committee on Research Funds, the School of Medicine, Yale University.

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EFFECT OF TOTAL HYSTERECTOMY UPON THE OVARY OF THE MACACUS RHESUS

An Experimental Study[1]

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THE uterus, that venerable organ which in one mood provides mankind with its first shelter, and in yet another subjects woman to a great proportion of her woes, is unique again with respect to its position in the realm of female sex hormonology. Stimulating no little investigation as to its part in the complex interplay of reproductive autocoids, and mirroring so acutely the effects of these cryptorhetic influences, it has as yet been assigned no definite rôle other than that of ancillary passivity, dominated and coerced, through the ovary, by that glandular autocrat, the anterior pituitary. Definitive evidence indicating an endocrine contribution on the part of the uterus would doubtless be as gratifying to the harassed clinician attempting to explain away an early post-hysterectomy menopause as it would prove stimulating to the endocrinologist.

The present experiments have been an attempt to shed some light on the subject from the experimental standpoint.

LITERATURE

Studies on the human ovary after hysterectomy are conspicuous largely for their lack of evidence. Werth (1902) described an increase in the size of the follicles with a conspicuous absence of follicular ova in human ovaries following hysterectomy, while Keitler (1904) observed what he considered a significant diminution in the number of follicles after excision of the uterus. Jacobsohn (1914) likewise reported fewer follicles present in the ovaries of hysterectomized women.

Vineberg (1915) and Hawks (1921) have described cystic ovaries found at a second operation following hysterectomy.

Lindig (1922) noted follicular enlargement following the removal of the uterus in women, while Terada (1921), in an experimental study, observed follicular atresia in the ovaries following hysterectomy. Schubert (1930) was able to find no ova after uterine excision.

Regardless of the discrepancies in the reported condition of the ovary after hysterectomy, there is general agreement among clinicians that removal of the uterus does hasten menopausal symptoms.

Sessums and Murphy (1932), in an analysis of 91 cases of hysterectomy with complete or partial conservation of ovarian tissue in women below 36 years of age, report the appearance of unmistakable subjective menopausal symptoms in 43 per cent before the age of 40 years.

Attempts to adduce evidence of the influence of the uterus on the ovaries from the purely experimental standpoint has been but little more convincing.

Marshall (1922) states that the ovary of the rabbit is found normal 10 months after removal of the uterus, and that hysterectomized females accept the male. Long and Evans (1922) could detect no effect from hysterectomy on estrus in the white rat. Hartman (1925) states that hysterectomy has no effect on the cycle in the opossum.

Removal of the uterus has no effect on the voluntary activity of the white rat as shown by Durant (1927), and Deanesley and Parkes (1933) have reported that hysterectomy is without effect on the estrous cycle of the ferret.

Siegmund (1933) found that the ovaries of young female dogs do not lose their ovulatory activity after hysterectomy, but cites the work of Zimmerman who found that hysterectomy in young bitches was followed by marked histological changes in the ovaries, characterized by disintegration of the eggs, formation of cystic follicles, follicular hematoma, and the absence of corpora lutea.

Probably the best substantiated evidence indicating that hysterectomy influences the

[1]This work was supported by a grant to Dr. Edgar Allen from the Committee for Research in Problems of Sex of the National Research Council.

ovarian cycle is the work of Leo Loeb (1927), who showed that hysterectomy following ovulation in the guinea pig results in persistence of the corpus luteum. More recently Asdell and Hammond (1933) have found that removal of the uterus in the rabbit is followed by prolongation of the life of the corpus luteum, and that this persistence of the corpus luteum is not merely of one form, but of partial function as well, since postcopulatory ovulation does not occur in these animals. The period of corpus luteum persistence is, however, much shorter in the rabbit than in the guinea pig.

Sessums and Murphy (1933), in a series of experiments on rabbits, state that hysterectomy in these animals tended to inhibit estrus and produced degenerative and inhibitory changes in the ovaries. These workers believe that endometrial autotransplants limit these inhibitory and degenerative changes, and conclude that the endometrium probably elaborates a hormone which influences the ovary.

Murphy (1934) failed to find any changes in the weight of the ovaries in the white rat following uterine excision.

Mavromati (1932) found that hysterectomy in rats was followed by prolonged estrus and that rats in which prolonged estrus occurred spontaneously showed atrophic uteri at autopsy. This worker felt that these results indicated that the uterus either destroys large amounts of theelin or inhibits its formation, and that with the withdrawal of this influence the excess of theelin continues to keep the vaginal epithelium in a stage of active estrus. Such a view seems scarcely tenable when one reflects that he used but 8 animals and does not mention such control conditions as diet and environment.

EXPERIMENTAL

Five female Macacus rhesus monkeys were used. Two of these were mature, having definite menstrual records and showing recent corpora at the time of operation. The 3 remaining were immature, as evidenced by size, history of no menstruation, immature type of "sex skin,"[1] and the absence of large follicles or corpora at operation. Total supravaginal hysterectomy and total bilateral salpingectomy was carried out in each animal. Ovaries from 4 animals, 2 mature and 2 immature, were studied for controls.

Operative procedure. The animals were anesthetized with ether and catheterized. The abdomen was shaved, prepared with iodine and alcohol, and draped with a sterile laparotomy sheet. A midline incision was made from just above the symphysis to a point 1 centimeter below the umbilicus. The peritoneum was carefully opened and the presenting viscera carefully packed away with gauze strips moistened in warm, sterile saline. The uterus was then picked up and measured at the level of the uterine horns. The ovaries were also measured, care being used not to injure them. The tubes were dissected free from the ovaries, meticulous precautions being taken not to disturb the ovarian blood supply. The broad ligament was divided between the abdominal wall and the uterus, division being carried to the point at which the peritoneum is reflected posteriorly over the rectum and anteriorly over the bladder.

At this point the uterus was elevated by means of an Allis clamp and the peritoneum stripped from the lower segment, the peritoneum being reflected backward and downward. The vagina was clamped off just below the cervix by means of a Kelly clamp and the uterus and cervix were removed. After carbolization, the stump was closed with a purse-string suture and the peritoneum was brought together and closed over the stump. After it had been determined that no bleeding was occurring the ovaries were carefully isolated from the surrounding viscera and the abdomen was closed by means of four rows of sutures. A collodion dressing was applied to the outer wound.

Following operation the monkeys were observed daily for color changes in the "sex skin," and vaginal lavages were done every second day. The animals were explored at intervals and measurements made of the ovaries as well as observations for large follicles and corpora lutea. At these times, care was taken in no wise to traumatize the ovaries.

[1] The term "sex skin," or "sexual skin," refers to the reddening and swelling about the genitalia. The term "sexual skin" was first applied by Langley and Sherrington (1891).

Vaginal lavage technique. The method used was that described by Hartman (1932). A uniform quantity of 2 cubic centimeters of physiological saline was used to make each lavage, the fluid being withdrawn and reinjected into the vagina three times. One cubic centimeter was withdrawn and placed in a vial and the sediment allowed to settle over a period of 12 to 18 hours. The amount of sediment was read at the end of this time by means of a scale.

Lavages were made on the average of three times per week.

At the end of the experiment, the animals were sacrificed and the ovaries removed and studied from serial microscopical sections. The number of normal, atretic, and polyovular follicles was counted and recorded in each case. Microscopical studies of the excised uteri and tubes were made, particular care being taken to obtain sections through the entire lower portion of the cervix at the line of amputation.

The pituitary glands were removed at autopsy and submitted to another investigator for later cytological studies.

OBSERVATIONS

From the amount of sediment in the vaginal lavage it was possible to determine the time at which a recent corpus luteum could be expected. This was confirmed in three instances by operation. The time interval between the points of highest sediment content was fairly constant for the individual animal.

Histological sections of the excised uteri showed that amputation of the cervix had been complete in every instance.

The condition of the ovaries from the time of hysterectomy until the termination of the experiment is recorded in the protocols.

A census of normal and atretic follicles found in the ovaries of the experimental animals is given, together with a census of control ovaries, in Table I.

Daily color records of the "sex skin" of the hysterectomized series showed no variation from the normal. Throughout the experiment the animals remained among the healthiest in the colony, and all showed consistent monthly weight gains.

PROTOCOLS

Monkey 21. This animal was considered before operation to be sexually immature because of the absence of menstruation and the pale color of the sex skin. This was confirmed at operation.

July 19, 1934. The uterus and both tubes removed. The right ovary measured 9 by 7 by 5 millimeters, left ovary 10 by 7 by 6 millimeters. No corpora were present, although both ovaries contained several follicles 1 millimeter in diameter.

September 7, 1934. Fifty days after hysterectomy, a laparotomy was performed. Dense adhesions were encountered. Both ovaries were firmly bound down. The right ovary measured 9 by 6 by 12 millimeters, left ovary 9 by 5.5 by 4.5 millimeters. No corpora or large follicles were observed.

October 31, 1934. Fifty-three days after the first laparotomy, and 103 days after hysterectomy, the animal was again explored. Abdominal adhesions were more marked than on the previous exploration, but the ovaries were no closer bound down than before. The right ovary measured 11 by 9.5 by 10 millimeters; left ovary 10.5 by 8.5 by 8 millimeters. The left ovary contained a recent corpus luteum and several well developed superficial follicles. The right ovary contained an old corpus luteum and several very small superficial follicles.

February 20, 1935. Two-hundred and sixteen days after hysterectomy the animal was sacrificed. Both ovaries were surrounded by rather dense adhesions. The right ovary measured 8 by 8 by 7 millimeters; left ovary 7 by 6 by 5 millimeters. No corpora were present.

High vaginal sediment levels occurred at 22, 23, 25, 26, 21, and 22 day intervals, in the order given.

Monkey 37. This animal was also thought to be, and later proved by operation to be, sexually immature.

August 6, 1934. A total hysterectomy and bilateral salpingectomy were carried out. The right ovary measured 11 by 5 by 9 millimeters; left ovary 12 by 6 by 11 millimeters. No corpora or large follicles were found.

October 29, 1934. Fifty-four days after hysterectomy, an exploratory laparotomy was performed and the ovaries measured. When the peritoneum was opened a formidable mass of adhesions was encountered. Both ovaries were completely swathed in dense fibrous adhesions and were freed with considerable difficulty. The right ovary measured 8 by 5 by 7 millimeters; left ovary 7 by 5 by 6 millimeters. No corpora or large follicles were found.

January 3, 1935. Ninety-six days after the first exploratory laparotomy and 150 days after hysterectomy, the abdomen was again opened. The ovaries were carefully freed from the surrounding adhesions and removed. The right ovary measured 12 by 9 by 8 millimeters; left ovary 10 by 9 by 8 millimeters. No corpora or large follicles were present. The blood supply to both ovaries was good. The high levels of vaginal sediment were found at 20, 16, 23, 20, and 18 day intervals.

Monkey 40. This animal had never menstruated, and this fact, together with the pale color of the sex skin, led us to classify the animal before operation as sexually immature. This impression was confirmed at operation.

July 25, 1934. The uterus and tubes were removed. The right ovary measured 9 by 5 by 5 millimeters and the left ovary 8 by 6 by 5 millimeters. No corpora or large follicles were present.

October 9, 1934. Seventy-six days after hysterectomy the animal was explored and the ovaries measured: right ovary, 10 by 7 by 6 millimeters; left ovary, 8 by 6 by 5 millimeters. No corpora or large follicles were found. Firm, dense adhesions were found surrounding both ovaries.

November 23, 1934. Forty-five days after laparotomy and 121 days after hysterectomy, the animal was killed and the ovaries measured: right ovary, 8.5 by 6 by 5 millimeters; left ovary, 8.5 by 6.5 by 7 millimeters. No corpora or large superficial follicles could be seen.

Vaginal lavages showed the greatest amount of sediment present at 30, 31, and 29 day intervals, in the order given.

Monkey 60. This animal was mature and menstruated regularly.

July 26, 1934. Total hysterectomy and bilateral salpingectomy were performed. The right ovary measured 11 by 9 by 7 millimeters, and the left ovary 9 by 7 by 6 millimeters. The right ovary contained one recent corpus luteum.

September 25, 1934. Sixty days after hysterectomy a laparotomy was performed and the ovaries examined. The right ovary measured 7 by 8 by 5 millimeters; the left ovary, 9 by 6 by 8 millimeters and contained one large follicle. No corpora were present in either ovary.

November 11, 1934. Forty-seven days after laparotomy, or 107 days after hysterectomy, the animal was again explored. (Note: the left ovary was free in the abdominal space; the right was bound down by adhesions). The right ovary measured 7 by 7 by 7 millimeters while the left measured 10.5 by 10 by 9 millimeters. There were no large superficial follicles in either ovary. The left ovary contained an old corpus luteum estimated as about 1 month old.

February 27, 1935. One hundred and ten days after the second laparotomy and 217 days after hysterectomy the animal was sacrificed. The right ovary measured 10 by 9 by 7 millimeters; the left, 11 by 7 by 6 millimeters. No corpora or large superficial follicles were found.

The greatest amount of sediment by vaginal lavages occurred at 27, 27, 31, 22, and 29 day intervals.

Monkey 93. This animal was a large, mature female with a definite menstrual history. Operation was performed July 23, 1934, and the uterus and tubes were removed. The measurements of the ovaries at this time were: right ovary 12 by 11 by 9.5 millimeters; left ovary 9 by 8.5 by 7.5 millimeters. There was present one recent corpus luteum in the right ovary and one large follicle in each ovary (3 millimeters in diameter). The uterus was very vascular and the tubes markedly hyperemic.

September 21, 1934. Sixty days after hysterectomy, a laparotomy was performed to ascertain the condition of the ovaries. Extensive adhesions were encountered, and some difficulty was experienced in locating the left ovary. The right ovary measured 8 by 6.5 by 6 millimeters and the left ovary was found to be 11 by 10 by 10 millimeters. No corpora were present in either ovary, but a large follicle was present in the left ovary.

December 3, 1934. Seventy-three days after laparotomy and 133 days after hysterectomy, the animal was sacrificed and the ovaries were examined grossly. The ovarian measurements were: right ovary 10 by 9 by 8 millimeters; left ovary 9 by 8 by 7 millimeters. No corpora or large follicles were present in either ovary.

By vaginal lavage the highest sediment levels appeared at 20, 17, 20, 25, and 25 day intervals, in the order mentioned.

EVALUATION OF STUDY

The literature concerning the effect of hysterectomy upon the ovaries is far from being in agreement. Clinical observers are unanimous in their opinions that the removal of the uterus is in many cases followed by the premature appearance of subjective menopausal phenomena, interpreted as indicating functional impairment of the ovaries. Concerning the appearance of the ovaries themselves, there is less agreement as to the type and degree of structural change found, but all observers report changes of one sort or another.

Experimental studies, while obviously incapable of contributing anything toward the subjective elements in the problem, tend to demonstrate for the most part that the removal of the uterus is without any marked effect upon the ovaries in the several species studied. The work of Loeb (1927), demonstrating persistent corpora up to 90 days after hysterectomy following ovulation, the studies of Asdell and Hammond (1933) indicating a similar persistence of the corpus luteum in the rabbit, and the findings of Sessums and Murphy (1933), indicating that hysterectomy in the rabbit is followed by degenerative changes in the ovary and that endometrial implants prevent the appearance of these changes, are the most suggestive, and certainly the best authenticated, of the work indicating

that hysterectomy does influence the ovary. However, it must be borne in mind that the rabbit is in many respects a notoriously capricious experimental animal. The significance of the work of Loeb and of Asdell and Hammond is not clear as yet.

Regardless of the histological variations that can be demonstrated in the ovaries of hysterectomized animals, the final proof of ovarian activity, or inactivity, must come from an investigation into the functional aspect of that organ. Fortunately, the ovary lends itself admirably to such a study. The maturation of ova, the development of follicles, and the formation of corpora lutea are all "anatomical footprints" left in the wake of physiological transpirations, and by them we are enabled to trace sequentially, as it were, the trail of functional events through that organ. The finding of corpora is *prima facie* evidence that the ovary is performing its normal function, viz.: that of ovulating; and the periodic examination of the ovary, together with a comparison of what we accept as the normal, enables us to detect variations in the rhythm as well as other changes.

The Macacus rhesus, like the female of the human species, runs a regular menstrual cycle with this exception—the summer months are normally anovulatory. The cycle averages 28 days (Hartman, 1932), and ovulation occurs normally from the tenth to sixteenth day after the onset of the last menstrual period, the average being on the thirteenth or fourteenth days (ibid.).

The "sexual skin" of the female Macacus rhesus undergoes periodic fluctuations in color intensity during the cycle. Throughout the follicular phase of the cycle there is a gradual increase in color up to a maximum, which is reached during the third week after the onset of menstruation. This is followed by a gradual subsidence of color intensity until just after menstruation, when, with the development of new follicles, the color again begins to increase. This has proved, in our experience, to be a valuable index of ovarian activity, for this coloring can be induced in ovariectomized monkeys by injections of ovarian follicular hormone (Collings, 1926; Allen, 1927).

Two questions present themselves in a study of this sort. (1) Does hysterectomy prevent the development of sexual maturity in the immature female monkey? (2) Does removal of the uterus influence the ovarian cycle of the sexually mature monkey? If either, or both, of these queries are answered in the affirmative, then the mechanism of that influence must be inquired into. Postulating for the sake of argument that excision of the uterus does influence the ovary, then two possible explanations present themselves: First, that the effect of hysterectomy on the ovary is a purely traumatic one, the damage to the vascular or nerve supply to the organ producing trophic changes. Second, that this disturbance is due to an endocrine relationship, as suggested by Sessums and Murphy (1933) for the rabbit.

An analysis of the protocols reveals that of the three immature females, one, No. 21, definitely went on to sexual maturity, as evidenced by the finding of a corpus luteum at laparotomy 103 days after removal of the uterus.

The 2 other animals in the immature group did not reach sexual maturity, as shown by the consistent lack of corpora or large follicles in the ovaries. Both these animals were smaller than monkey No. 21, and it is our opinion that these animals would have developed into sexual maturity if sufficient time had been allowed before sacrificing the animals. It should be mentioned that there was no significant reduction in the size of the ovaries and no changes could be detected grossly.

Of the mature group, monkey No. 60 gave clear cut evidence of ovulatory activity at laparotomy. Monkey No. 93 showed one large follicle ready to rupture at laparotomy 60 days after hysterectomy.

A consideration of the census of follicles found in the ovaries at the completion of the experiment (Table I), compared to ovaries from the control group, reveals no significant differences.

The percentage of follicles with antra was about the same for both the experimental and the control groups. There was a comparable amount of follicular atresia in the experi-

TABLE I.—INCIDENCE OF NORMAL AND ATRETIC FOLLICLES IN OVARIES OF HYSTERECTOMIZED MONKEYS COMPARED TO NORMAL

Monkey No.	Ovary	Types of follicles				Polyovular	Percentage of atretic follicles
		Atretic		Normal			
		Small	Large	Small	Large		
Experimental							
21—Immature	Right	76	25	230	77	4	24.7
93—Mature	Left	66	14	5	4		89.0
40—Immature	Right	76	20	50	17	6	59.0
60—Mature	Right	76	39	756	50	2	11.0
37—Immature	Left	88	11	251	19	10	25.0
Control							
33—Mature	Left	28	45	260	66	1	19.0
47—Immature	Left	114	44	463	47	15	27.0
35—Mature	Left	64	26	204	34	0	27.0
14—Immature	Right	30	30	175	39	0	22.0

mental and control immature animals, but considerable variation was found in the percentage of atresia in the mature groups. This latter fact, however, is to be expected since animal No. 93 had recently ovulated, the ovaries from monkeys Nos. 33 and 35 were removed in the middle of the cycle, and since monkey No. 60 had shown a high sediment level in the vaginal lavage 10 days before operation. Certainly there was no evidence of increased follicular atresia in either the mature or immature animals upon which hysterectomy had been performed.

It will be noted that frequent mention is made in the protocols of the rather dense fibrous adhesions found surrounding the ovaries. It seems of no little significance to the writers that although adhesions were marked on superficial examination in every instance, yet in only one animal (No. 93) were the ovaries completely encompassed by adhesions. In each of the remaining eight ovaries a considerable portion of the surfaces of the ovaries were free, and closer scrutiny revealed the ovary lying for the most part in a small peritoneal pocket. It is interesting to speculate upon the relation of the intact capsular epithelium of the ovary to its retention of normal function.

SUMMARY AND CONCLUSIONS

Five female monkeys (Macacus rhesus), including mature and immature animals, were totally hysterectomized and the effect on the ovaries studied. The animals were followed for periods ranging from 121 to 217 days after hysterectomy. No impairment of ovarian activity could be detected by vaginal lavage studies, "sex skin" color records, or examination of the ovaries at laparotomy. A postmortem census of the follicles in the ovaries revealed no increase in follicular atresia for either the mature or immature group. One immature animal went on to definite sexual maturity 103 days after hysterectomy. It is concluded that hysterectomy in the Macacus rhesus is without effect upon the ovary, except for purely traumatic effects. The monkey affords no evidence that the uterus contributes any endocrine influence upon the ovary.

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THE ANOMALOUS RIGHT SUBCLAVIAN ARTERY

Its Practical Significance; with a Report of Three Cases[1]

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IRREGULARITIES in the development of the major branches of the aortic arch are numerous indeed, and have been conveniently classified by Poynter (1916) as follows: (a) branches fewer than normal as in the occurrence of bi-innominate arteries; (b) branches more numerous than normal, as in the absence of the innominate, and consequent separate origin of both carotid and subclavian arteries; (c) branches in abnormal succession, dependent upon an irregular development of the aortic-arch plan. The cases which we shall report belong to this last named group; in them the right subclavian arises not first, or in conjunction with the carotid of the same side, but as the last direct branch of the aortic arch (Figs. 1 and 5, 6 and 7). They are not uncommon, occurring in 1 in 120 cases.[2]

Our 3 cases of anomalous right subclavian artery were encountered in the course of routine laboratory dissection of 102 specimens[3]; since they are essentially similar, one will serve as basis for description.[4] The first branch of the arch of the aorta was the right common carotid artery; it was followed in succession by the left common carotid, left subclavian, and (anomalous) right subclavian, all arising separately from the arch in the order named, from before backward. The first three branches in specimen I (Figs. 1 and 2) were placed, at their origin, in almost parasagittal plane; in specimens II (Fig. 7) and III the first branch lay appreciably to the right of the succeeding two. In the 3 cases the two anterior trunks arose very close together; the second was separated from the third by a slight interval; between the latter and the anomalous vessel a greater one occurred in which the esophagus lay. The anomalous subclavian artery in the 3 cases originated from the aorta at the level of the midportion of the third thoracic vertebra[5]; it ascended dorsal to the esophagus, to attain the right side of the vertebral column opposite the first thoracic vertebra. The right recurrent laryngeal nerve arose from the trunk of the vagus opposite the cricoid cartilage (Figs. 1 and 5).

The arrangement of aortic trunks and their visceral relations are dependent upon the aberrant development of the aortic arch system in the embryo.

Usually, as has been described with admirable completeness by Congdon (1922), the transformation of the aortic arch system involves the interruption of the right dorsal aorta (right fourth aortic arch) caudal to the origin of the primordial right subclavian artery (Fig. 3, at asterisk), so that the subclavian arises either separately as the first branch of the arch, or in conjunction with the right common carotid, through the innominate as intermediary. But, in the type of anomalous origin represented in our specimens, the interruption occurs at a higher level, cephalad to the origin of the right subclavian (Fig. 4, at asterisk) so that the latter vessel then arises from the hinder part of the arch, just beyond the origin of the left subclavian artery[6]. This caudal segment of the right dorsal aorta, now incorporated into the right subclavian artery instead of becoming obliterated, is dorsally placed, and, in the body of embryo is already established in the characteristic retro-esophageal location. Since the fourth right

[2]An incidence reported by Cairney (1925) in summarizing the results of eight investigators who find 19 in 2291 cases; Cobey (quoting Thompson) reports 1 per cent; Harvey reports 0.8 per cent, Holzapfel 0.6 per cent. Since the publication of Cairney's results at least 11 cases, exclusive of those in the present paper, have been reported in the literature: one each by Shellshear and Anderson (1927), Kirch (1927), Windle *et al.* (1928), Golub (1929), Priman (1929), Speschilow (1930), De Garis (1932), Funck-Brentano (1934), Huard *et al.* (1934); 2 by Dolgopol (1934).

[3]Two in 34 specimens during the winter quarter of 1934, 1 in 68 during the autumn and winter quarter of 1934–35; no others had been encountered in our laboratory since that reported by Windle (1928), making a total of 4 in 470 specimens. No other aortic-arch anomalies were found during the 8 years.

[4]They may, for purposes of identification, be designated specimens I, II, and III. The relevant anatomy of specimen I is illustrated in Figures 1, 2, and 5, that of specimen II in Figures 6 and 7; specimen III is not represented in the illustrations. Specimen I, white male, aged 50 years, height 5 feet 8 inches, weight 150 pounds; specimen II, white male, aged 70 years, height 5 feet 9 inches, weight 150 pounds; specimen II, black female, aged 45 years, height 5 feet 7 inches, weight 100 pounds.

[5]In specimen I the branches of the anomalous right subclavian artery were, in succession: vertebral, superior intercostal (no record of inferior thyroid), deep cervical, internal mammary, transverse cervical (no record of transverse scapular). For specimens II and III, no record of the subclavian branches were available.

[6]According to Poynter (1916) and Cairney (1925), who have provided very comprehensive studies of all aortic-arch anomalies.

[1]Contribution No. 224 from the Anatomical Laboratory of Northwestern University Medical School.

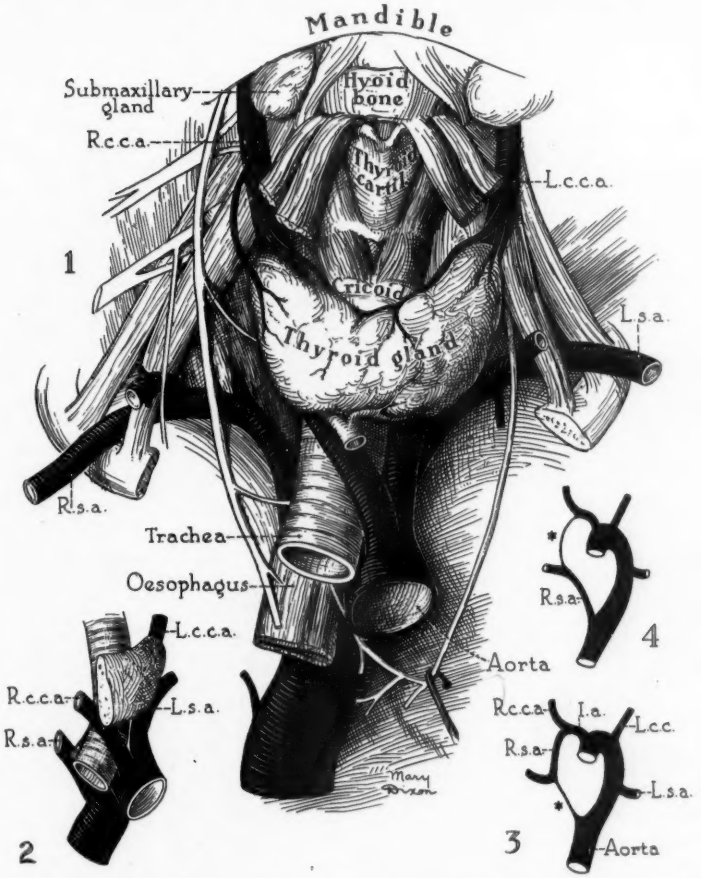

Fig. 1. The deep structures of the neck and upper portion of the thoracic mediastinum in ventral view (specimen I). The platysma and sternocleidomastoid muscles, the cervical fascia, superficial vessels and nerves, and deep veins have been removed to expose the great arteries arising from the aortic arch; the sternohyoid and omohyoid muscles have been cut. Showing the location of the anomalous right subclavian artery, dorsal to the esophagus, and the retrothyroid position of the right common carotid artery (cf. Fig. 4). *L.c.c.a.*, Left common carotid artery; *L.s.a.*, left subclavian; *R.c.c.a.*, right subclavian artery. ×.44 natural size.

Fig. 2. A portion of the area illustrated in Figure 1 showing the right common carotid and anomalous right subclavian arteries with their chief visceral relations as revealed by removal of the right lobe of the thyroid gland (cf. Fig. 1). Note, on the right side, the ventrodorsal succession of thyroid gland, common carotid artery, trachea, esophagus, anomalous subclavian artery. ×.22.

Fig. 3. Diagram of the aortic arch system in the 18 millimeter human embryo, showing the formation of the usual arrangement of branches from the arch (after Congdon, Figs. 14, 15). Asterisk marks the short caudal segment of the right aortic arch which will disappear; the cranial segment will become the right subclavian branch of the innominate artery (as in Fig. 8, normal adult arrangement). *I.a.*, innominate artery; other abbreviations as before. ×.22.

Fig. 4. Diagram to show the formation of the anomalous right subclavian artery (labeled) as the last branch of the aortic arch; the segment between common carotid and subclavian disappears; there is no innominate artery.

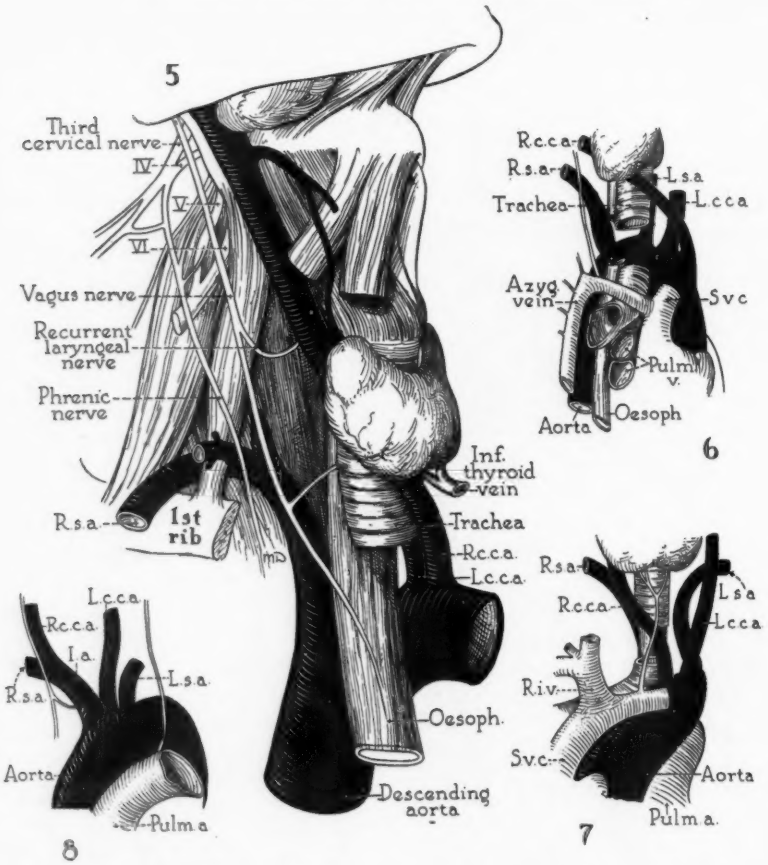

Fig. 5. The structures illustrated in Figure 1 as seen in ventrolateral view. Showing particularly the relation of the right common carotid to the thyroid gland and trachea, and of the anomalous right subclavian artery to the esophagus. ×.44.

Fig. 6. The deep structures of the neck and upper portion of the thoracic mediastinum in lateral view (specimen II). Sections of the trachea and esophagus have been removed to reveal the situation and course of the anomalous right subclavian artery; the right recurrent laryngeal nerve is not looped around the latter vessel. ×.22.

Fig. 7. The same structures in ventral view. Showing the relations of the carotid and subclavian arteries. The left innominate vein has been cut just beyond the point at which it receives the inferior thyroid vein; a section of the trachea has been removed to show the esophagus as it lies in front of the right subclavian artery. ×.22.

Fig. 8. The order and relations of the arterial trunks from the aorta, in a normal case. Contrast with Figure 2 showing anomalous arrangement, and compare with Figure 3, representing mechanism of origin. ×.22.

aortic arch is lost in this transformation the inferior laryngeal nerve of the right side passes directly to its termination, without passing around the right subclavian artery (compare Figs. 6 and 8).

As a result the anomalous vessel is situated dorsal to the esophagus (esp. Figs. 1, 2, and 5), instead of ventral to the trachea; the first vessel from the arch—the right common carotid artery—is drawn into a location beneath the corresponding lobe of the thyroid gland (Figs. 1 and 5); the recurrent laryngeal nerve of the right side follows a direct

high course from the vagus nerve to the larynx (Figs. 1 and 5). The right subclavian artery is, then, not encountered on an anatomical level just dorsal to that of the innominate veins, but in retro-esophageal position against the vertebral column; the course of the right common carotid artery is not wholly to the right of the midline of the neck, but transtracheal, in a direction upward and toward the right; the recurrent laryngeal nerve does not descend to a clavicular level at the root of the neck, but only as far as the midthyroid level.

Various clinical symptoms may arise from the relation of the anomalous vessel to surrounding structures; visceral pressure upon the right subclavian artery may produce inequality in radial pulses according to Harvey (1917) and others; through the same mechanism enlargement of the thoracic duct may occur; Cobey (1914) points out that, owing to pressure exerted upon the artery by the esophagus, its symptomatology may be confusingly similar to that of cervical rib; he infers that trophic changes in the upper extremity might follow. Quain, long ago, mentioned dysphagia as one of its symptoms, citing a case history. In surgery of the cervical region it may prove of importance in ligation of the subclavian artery because of the depth at which the vessel is situated (Goldbloom). In surgery of the upper esophagus (Harvey), and, in fact, in any approach to the right side of the neck, the peculiar position of the inferior laryngeal nerve would prove baffling. Certainly in 2 of our cases (Figs. 1 and 6) the relations of the common carotid artery to the right lobe of the thyroid gland would have been an anatomical condition fraught with surgical danger had a thyroidectomy or a low tracheotomy been performed.

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TUMORS OF THE SPERMATIC CORD, EPIDIDYMIS, AND TESTICULAR TUNICS

Review of Literature and Report of Forty-One Additional Cases

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TUMORS of the testis are relatively rare. They constitute 5.8 per thousand of all malignant tumors of men, according to the mortality statistics of the United States registration area. Similarly, tumors of the epididymis are exceptionally rare, in fact so rare that their existence might seem of more academic than clinical importance. Other intrascrotal tumors of interest, which occur more frequently, include those of the spermatic cord and the testicular tunics.

The majority of tumors of the epididymis, spermatic cord, and testicular tunics are of the benign type and hence the prognosis is quite different from that of testicular tumors. It seems worth while, therefore, to call attention to this group of cases. This paper reviews the literature and presents 41 such cases seen at the Mayo Clinic before January 1, 1935. Among the 41 cases there were 26 tumors of the spermatic cord, 13 of the epididymis, and 2 of the tunica vaginalis.

Hinman and Gibson, in 1924, reviewed the literature up to that time and added 3 cases which they had observed. These are included in the following review.

TUMORS OF THE SPERMATIC CORD

According to Patel and Chalier, the earliest known tumor of the spermatic cord was recorded by Cloquet in 1819. This was a lipoma and may not have been truly a tumor of the cord for the report is meager. Patel and Chalier collected 110 cases of tumor of the spermatic cord in a very complete review of the literature. Among these were the following: lipomas, 37; sarcomas, 22; mixed tumors, 33; fibromas, 12; myomas, 5; and carcinoma, 1.

Rubaschow (35), in 1926, reviewed the literature again and listed the following tumors of the spermatic cord reported up to that time: teratoma, 1; dermoids, 13; mesodermal tumors, that is, myxolipomas, myxofibromas, myxofibrolipomas, myxofibrosarcomas, and so forth, 27; cysts of the wolffian body, 15; carcinomas, 3; lipomas, 57; fibromas, 24; myxoma, 1; sarcomas, 24; connective tissue cysts, 8; lymphangiomas, 4; and tumors of undecided origin (description inadequate), 6, or a total of 183.

MacKenzie, in 1932, in reporting a case of fibromyxosarcoma, discussed 14 additional cases which he had found in a review of the literature. MacKenzie included a case described by Oehlecker as a tumor of the spermatic cord, which I believe should be classified as a tumor of the tunica vaginalis and it is so classified in this review. He failed to include cases reported by Fritzler, 3 cases of lipoma and 1 of sarcoma; by Starlinger, in 1925, a case of myxofibroma; by Romiti, in 1927, 3 cases, 1 of fibrosarcoma, 1 of myxolipoma, and 1 of malignant tumor of connective tissue origin; Ssinelščikowa, in 1929, a rhabdomyosarcoma of a youth 15 years of age; by Allende and Gonzalez, in 1930, a sarcoma; by R. Scotte Douglas, in 1930, a spindle cell sarcoma. Since the appearance of MacKenzie's article, cases have been described by Monserrat and Galvez, in 1932, a case of fibroblastic sarcoma of the cord; by Cilento, in 1932, an angioma; by Deutsch, in 1933, a fibroma; by Gioia, in 1933, a case of fibroma; Gioia also mentioned in his article a case reported by Odena in which the tumor, a lipofibrosarcoma, weighed 8.5 kilograms. In 1934 Hirsch reported a rhabdomyosarcoma, Leriche a reticulosarcoma and Fresnais and Mouchet a sarcoma. These cases, added to those of MacKenzie's review, would bring the total number of tumors of the spermatic cord which have been so far reported, to 216.

It is probably not commonly appreciated that these tumors sometimes attain enormous

size. The largest growths, composed purely of lipomatous tissue or of a mixture of tissues, so called myxolipomas or myxofibrolipomas, may become quite annoying because of their size. The case of Mazzini is one of the largest; the tumor, which completely obscured the genitalia, was larger than the patient's head. Dermoids of the spermatic cord also attain fairly large proportions.

Growth of the majority of tumors of the spermatic cord is extremely slow. As a rule they are not painful, and frequently the patient is not aware of their existence until the trauma calls attention to them. Following this they are, in most instances, allowed to attain an appreciable size before medical advice is sought, at which time the weight of the tumor causes local discomfort and perhaps a drawing pain in the groin.

Benign tumors. Approximately 70 per cent of these tumors of the spermatic cord are benign, as can be seen in the lists that have been given earlier in this paper. Of the benign tumors, the lipomas, mixed mesodermal tumors, and fibromas make up the bulk of the group.

The malignant tumors are almost exclusively sarcomatous in type. Only 3 cases of carcinoma have been reported. Rubaschow (37) reviewed these cases and concluded that the growths probably originated from cell-rests of the wolffian body. No cases have been reported of neoplastic proliferation of the epithelium of the ductus deferens.

It appears, then, that the majority of these tumors of the spermatic cord are benign, according to the reports in the literature, and this coincides with the experience at the Mayo Clinic, where, up to January 1, 1935, 24 patients suffering with benign tumors and 2, with malignant growths, were observed. In 21 cases, the enlargement proved to be a lipoma of the spermatic cord. The tumors varied from 2 to 8 centimeters in diameter. The youngest patient was 33 and the oldest 67 years of age.

Lipoma is the most commonly found tumor of the spermatic cord. However, it does not occur with the frequency that might be expected when the fatty growths that have been encountered in the inguinal region are recalled to mind. Such growths spring from the subserous fat around the margin of the internal inguinal ring, and in enlarging they grow along the inguinal canal, distending it; often the growths follow the spermatic cord as far as the scrotum. In many cases these growths act as predisposing causes of hernia, not only because they distend the inguinal canal and the internal and external rings, but they will, by propulsion, produce an infundibulum in the peritoneum and thus a hernial sac.

When the growth is small, it is easy to distinguish at operation between the true lipoma of the spermatic cord and the more common lipoma of the properitoneal fat. If, however, the tumor is large, it is often impossible to say that its origin is not from the spermatic cord. A lipoma of the spermatic cord always should be surrounded by the tunica vaginalis communis and should derive its main blood supply from the vessels of the cord, but in time the true lipoma of the cord often will break through the tunica vaginalis communis and will connect so closely with the properitoneal fat that it appears to be of that origin.

In this series of 21 cases of lipoma of the spermatic cord, there were 14 cases in which there was associated inguinal hernia. In 5 cases there were apparently bilateral tumors, all in association with hernia. It is my impression, from study of the records of these cases, that all of the growths were true lipomas of the spermatic cord. Since more than 7,000 operations for inguinal hernia have been performed at the Mayo Clinic in the period covered by this review of tumors of the spermatic cord, it can be seen that the incidence in this experience is not high. In every instance the surgeon gave the opinion that the lipomas originated from the spermatic cord.

Microscopically the tumors were composed of fat tissue no different from that seen elsewhere in the body.

Considering these 21 cases as instances of true lipoma of the spermatic cord, the approximate incidence of lipomas compared to all tumors of the spermatic cord recorded in the literature, and included in this paper, is about one to three, since there were 82 lipomas out of a total of 242 tumors of the spermatic cord (33.8 per cent).

Fibroma of the spermatic cord occurs about a third as frequently as lipoma. Rubaschow (37) listed 24 cases which he collected from the literature, and since that time only 3 other cases have been reported; namely, by Gioia and by Deutsch.

Fibromas of the spermatic cord are usually small, but cases have been reported in which the size attained was unusual, and in 1 case the tumor weighed 15 kilograms.

According to Patel and Chalier and Rubaschow (37), the origin of these fibromas appears to be in that portion of the spermatic cord that is near its juncture with the epididymis, and they arise from the connective tissue which unites the various elements of the cord at that point. They are slow growing and cause no symptoms other than the swelling. This is indicated by the fact that the majority of the patients give histories of having noted the tumors for a number of years before seeking medical attention; the average interval is 6 years.

CASE 22[1]. A man, 28 years of age, as long as he could remember, had noted a mass in the right inguinal region near the external inguinal ring. He was certain that it had not increased in size for many years. He was advised to have it removed. At operation the growth was found to be attached to some of the spermatic veins. It was lobulated, measured approximately 4 by 3 by 2 centimeters, and weighed, when excised, just 14 grams. On gross appearance it was firm and on inspection of its cut surface, seemed fibrotic. Microscopic examination proved it to be a fibroma. Convalescence was uneventful and the patient was alive and well when heard from 4 years later.

True myxoma of the spermatic cord is an extremely rare type of tumor. The case of Schulter is the only one in which the growth can be correctly termed a myxoma. Rubaschow (37) reported 27 cases which he classified as tumors of mesodermal origin. These were reported by the various authors as myxolipomas, myxofibromas, myxofibrolipomas, myxosarcomas, myxochondrosarcomas, myxocystosarcomas, osteomas, osteosarcomas, and fibroliposarcomas. To these should be added similar cases reported by Starlinger, Romiti, and MacKenzie. That many of these tumors are relatively benign is suggested by the case included in MacKenzie's review reported by Mazzini in which the growth, a lipofibromyxoma, attained huge size without apparent toxic effect. It is safe to say that not more than half of these combined tumors are very malignant in character.

Patel and Chalier collected from the literature reports of 5 cases of myoma of the spermatic cord. One of the patients seen at the Mayo Clinic could be considered to have had a myoma. However, because the growth recurred, and because there were, in some portions, rather numerous mitotic figures, it was classed as a myosarcoma of low grade of malignancy. Myomas arise in the region of the juncture of the ductus deferens and the epididymis, and in most cases are adherent to both. Muscle fibers of the cremasteric internus muscle are the apparent origin. They do not attain the huge size of the lipomas and are more firm on palpation but not as hard as fibromas.

Vascular tumors, such as lymphangiomas, arising in the spermatic cord, are rare. MacKenzie listed 5 cases and to these should be added a case reported by Cilento.

CASE 23. A boy, 5 years of age, was brought to the Mayo Clinic with a complaint of ear trouble. This was cared for, but routine physical examination disclosed a small mass in the left side of the scrotum, well above the testis. Excision was advised, and at operation the mass, 1 centimeter in diameter, was found attached to the spermatic cord just below the external inguinal ring. On microscopic section it proved to be a hemangioma. Convalescence and the subsequent course were uneventful.

Only 13 cases of dermoid cyst of the spermatic cord are included in Rubaschow's report. No other cases have been recorded since then. The spermatic cord is an unusual situation for a dermoid cyst. Theoretically, these cysts arise from the primitive ectodermal cells displaced in the embryo from the lumbar region through the wolffian body. These cells accompany that organ, as rests, in its ultimate transition to the ductus deferens. In none of the cases reported was a diagnosis of dermoid made before operation.

Benign cystic tumors of other nature include those arising in cell rests of the wolffian body and those in which the origin is uncertain, apparently arising from connective tissue

[1] Cases 1 to 21 were lipomas of the cord.

adjacent to the spermatic cord. One such case was encountered at the Mayo Clinic and is described as follows:

CASE 24. A man, 56 years of age, came for general examination. This revealed, among other abnormalities, a small lump in the right side of the scrotum, apparently attached to the spermatic cord well above the upper pole of the testis. After his attention was called to it, he admitted having known of its presence for years, but he had attributed no significance to it. In the absence of symptoms he refused operation. Two years later he returned, stating that he thought the growth had undergone recent enlargement, but examination did not confirm his impression, in the opinion of the examining physician. However, he asked to have it removed. Operation was performed through a scrotal incision, and an encapsulated growth, 2 centimeters in diameter, was found attached to the cord, well above the globus major of the epididymis. On microscopic section the growth proved to be a cystadenoma and apparently originated in connective tissue.

Malignant tumors. The most frequently occurring malignant tumor of the spermatic cord is the sarcoma. Twenty-four cases were reported up to 1926, and since then cases have been reported by Fritzler, Romiti, Karo, Allende and Gonzalez, Douglas, Leriche, and Fresnais and Mouchet. Beyond any doubt, under the heading of malignant tumors, should be included also many of those tumors which are in part sarcomatous; such as myxosarcomas, liposarcomas, chondrosarcomas, fibrosarcomas, rhabdomyosarcomas, and various other combined growths. The malignant nature of these tumors is sometimes overlooked. It is impossible to estimate the grade of malignancy from a study of photomicrographs that accompany the articles. Careful cytological study no doubt would disclose that some of them were relatively benign; however, the possibilities of transition in cell character as a result of stimulation by irradiation or injury always should be kept in mind and the growths treated accordingly. Treatment ought to be similar to that employed for malignant tumors, with subsequent periodic observation. In cases of highly malignant sarcoma, the clinical course parallels that of the most malignant tumors of the testis.

Two cases of malignant tumor of the spermatic cord encountered at the Mayo Clinic follow.

CASE 25. A man, 68 years of age, was first seen March 15, 1928, when he complained of bilateral inguinal hernias which he stated had been present for 12 years. He had worn a truss for these hernias, and 4 months previously he had noted a hard lump forming at the right external inguinal ring, which was tender when the truss was in place; therefore he had discontinued use of the truss. Examination disclosed a mass the size of a large plum (about 5 centimeters in diameter) at the right external inguinal ring. It was firm and did not transmit light. Roentgenograms of the thorax and spinal column were negative. In addition to the tumor there were bilateral inguinal hernias. Physical examination otherwise gave essentially negative results. A diagnosis of bilateral inguinal hernia and of tumor of the right spermatic cord was made, and operation was advised. Right herniotomy and right orchidectomy were performed April 10, 1928. A large tumor was found just at the external ring and extending over the symphysis pubis, arising from the cord 4 inches (10 cm.) above the testis. Castration was performed and a portion of the cord was removed. The hernial sac was excised and the canal completely closed by suturing the internal and external oblique muscles down to Poupart's ligament. The tumor removed is represented in Figure 1a. Examination disclosed that the growth was very firm. On cut section, in the gross, it had a yellowish-white, striated appearance such as is seen in uterine fibroids. The testis, epididymis, and ductus deferens were not involved. The tumor was very intimately attached to the spermatic cord.

Microscopic section disclosed what seemed to be a typical fibroma; on close examination of the section, however, it was seen that the tumor, in some places, was cellular, and here and there a rather large cell appeared, of a type that is never seen in a typical fibroma such as, for instance, a uterine fibroid. Because of this appearance the diagnosis of fibrosarcoma of malignancy grade 1 was made (Fig. 1b).

The patient had an uneventful convalescence and returned home after 3 weeks, feeling well.

The patient returned to the clinic 1 year later, or in May, 1929, complaining that 3 months after operation he had noted a recurring mass in the right inguinal region. This had grown to approximately 10 centimeters in diameter in the 9 months following, a size much greater than the original tumor. A diagnosis of recurrent malignant tumor was made and treatment by roentgen-rays and radium was given. The mass continued to enlarge, and 2 months later attained such a size that it extended across the entire right lower quadrant of the abdomen. The decision was made that the only justifiable treatment was further irradiation, and this was given, but without result. The patient died at home on September 14, 1929.

Postmortem examination was made elsewhere, but details of the findings were not obtainable. A microscopic section of the recurrent tumor in the groin is shown in Figure 2. It can be seen that these

cells bear very little, if any, resemblance to those of the original tumor. The tumor is a fibrosarcoma, grade 3.

It is interesting but hardly profitable to speculate as to what caused the transition from a tumor of malignancy grade 1, to a tumor of which the malignancy was grade 3 in the case just reported. Sarcomas of low grade of malignancy occasionally are observed to undergo change as a result of injury. The probabilities are that there was local extension of a more malignant type of cell at the time of removal of the original tumor which, however, could not be seen at operation.

CASE 26. A man, 33 years of age, was first seen at the Mayo Clinic December 9, 1920, at which time he stated that he had been operated on in 1914, and again in 1917, for the removal of tumors from the left groin. These had been the size of a hen's egg (about 6 cm. long) and the size of an olive (about 3 cm. long) respectively. He was not told what the nature of the tumor was considered to be, but roentgen treatments were given after their removal. Further swellings were not noted until 2 years later, when a tumor the size of a pea (about 1 cm. in diameter) appeared in the left inguinal region and began slowly to increase in size. Two months before he came to the clinic he was given three treatments by roentgen-rays and radium. This did not affect the size of the growth. It was not painful and caused no symptoms; the swelling was the only abnormality.

Examination revealed an irregular, hard, firm tumor, measuring 6 by 2.5 centimeters, situated in the upper part of the scrotum and adjacent to the left external inguinal ring. The testis and epididymis could be palpated separately and did not seem involved. All other physical examinations gave essentially negative results, including roentgenograms of the thorax and bones. A diagnosis of tumor of the spermatic cord was made and operation was advised.

Operation was performed December 20, 1920, by Dr. C. H. Mayo. A mass the size of a lemon (about 7 cm. long) was found involving the spermatic cord. The testis and cord were removed high in the inguinal canal.

The tumor removed is represented in Figure 3a; there were five separate lobulated masses, the smallest of which was 2.5 centimeters in diameter and the largest, 4 centimeters in diameter. The tumor was pinkish white and very firm. On cut section in the gross it looked fibrous. On microscopic section the tumor was a typical myoma except that in places there were rather large cells, and mitotic figures could be found here and there. Figure 3b represents an area such as makes up the greater portion of the tumor.

The patient was given a treatment with radium because of the history of repeated recurrence, and returned home feeling well. He was seen at the clinic again in August, 1923, or almost 3 years later, when he stated that a recurrence had been developing since December, 1921. On examination, a mass of firm consistency, measuring 10 by 4 centimeters, was found occupying the left half of the scrotum and extending up into the inguinal region. Examinations otherwise gave negative results, including roentgenograms of the thorax. A diagnosis of recurring tumor of the groin was made.

August 24, 1923, the tumor was excised widely. It involved the left groin and upper part of the scrotum, and when removed measured 7 by 4 by 4 centimeters, was very firm, and weighed 70 grams. On microscopic sections its structure was found to be very similar to that of the original growth, except that the cells were a little larger and the mitotic figures seemed of more frequent occurrence. Figure 4 represents an area that is fairly typical of the entire tumor; the diagnosis was myosarcoma, grade 1.

The patient was given high voltage roentgen therapy and went home one month later. In a letter, received from him recently, he stated that he is in good health, and that the tumor has not recurred again.

TUMORS OF THE EPIDIDYMIS

Benign tumors. Benign epithelial tumors of the epididymis are exceptionally rare. Sakaguchi, in 1916, reported an adenoma of the epididymis of a man, aged 32 years, who was operated on for long-standing thickening of that organ. He referred to the tumor as an adenomyoma, the principal tissue was glandular epithelium. This case is the only one of its type reported in the literature. Report of a case of benign tumor of the epididymis in which the predominating histological picture was that of epithelial hyperplasia follows.

CASE 27. A man, 54 years of age, entered the Mayo Clinic with a complaint of a nodule which had been present in the right side of the scrotum for approximately 25 years. It had not caused symptoms until recently, when he had noted pain in the right testis and groin. Examination revealed a nodule approximately 2 centimeters in diameter in the upper pole of the epididymis. Operation was advised. The nodule proved to be attached to the epididymis and on the insistence of the patient unilateral castration was performed. The testis proved normal. Microscopic section of the nodule revealed it to be a cystadenoma.

Lipoma is an exceptionally rare type of tumor; Wilbolz has given the only report of a case up to the present time. The epididymis normally does not contain fat, although occasionally a little may be found in the coverings

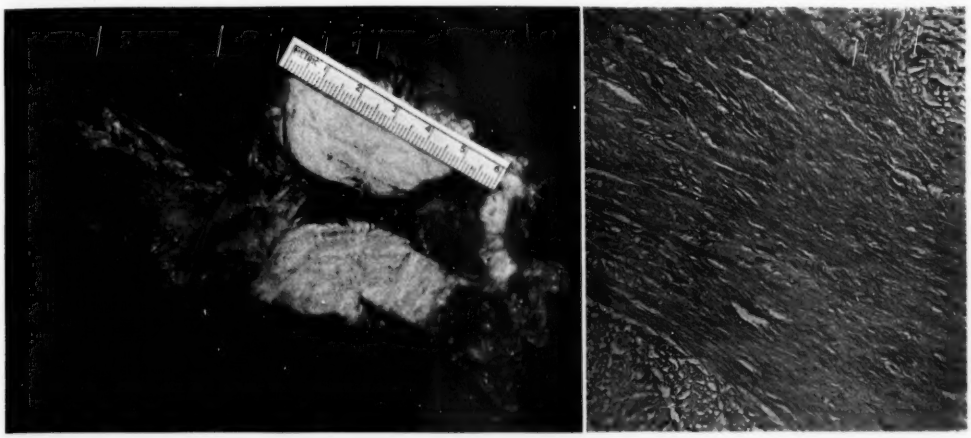

Fig. 1. a, left, Fibrosarcoma of spermatic cord; b, section of same tumor; malignancy was graded 1. ×60.

of connective tissue. In Wilbolz's case the tumor apparently originated from fat in the connective tissue coverings as on section several small lobules of fat, varying in size from 5 to 7 millimeters in diameter, were found. The pre-operative diagnosis in his case was epididymitis. Lipoma of the epididymis is so rare that it is of no clinical importance.

Myoma is the most common benign tumor of the epididymis if the site of origin can be proved satisfactorily to be in the epididymis. Rubaschow (35), however, expressed the belief that these tumors arise from adjacent structures and not from the epididymis. This is mere speculation, unless one has the opportunity of examining the tissue. Hinman and Gibson listed 6 cases of leiomyoma which they collected from the literature and which seem acceptable. To these should be added those of Eisenstaedt and Fischer, as these tumors certainly seem to have originated in the epididymis.

The epididymis has been said to have been the site of origin of fibromas in several cases reported. The tumors, however, originated in the caudal portion of the spermatic cord rather than in the epididymis and hence should be classed as tumors of the spermatic cord. Hinman and Gibson and Rubaschow concluded, after careful study, that there is no report in the literature of an unquestionable case of fibroma of the epididymis. There has been none since their articles appeared.

Of the vascular tumors of the epididymis, Conforti, in 1910, reported a case of lymphoendothelioma; Hardouin, in 1911, a case of angioma; Rigano-Irrera, in 1925, a case of lymphangioma, and Marcandier and Thomas, in 1930, a lymphangioma. All these seem to be authentic, the tumors arising in the epi-

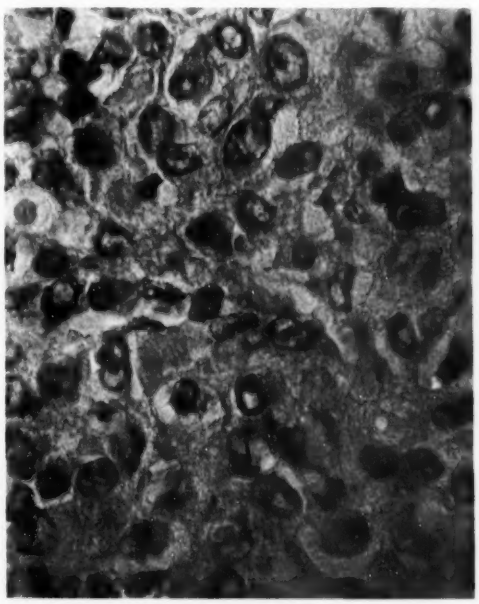

Fig. 2. Fibrosarcoma, grade 3. ×500.

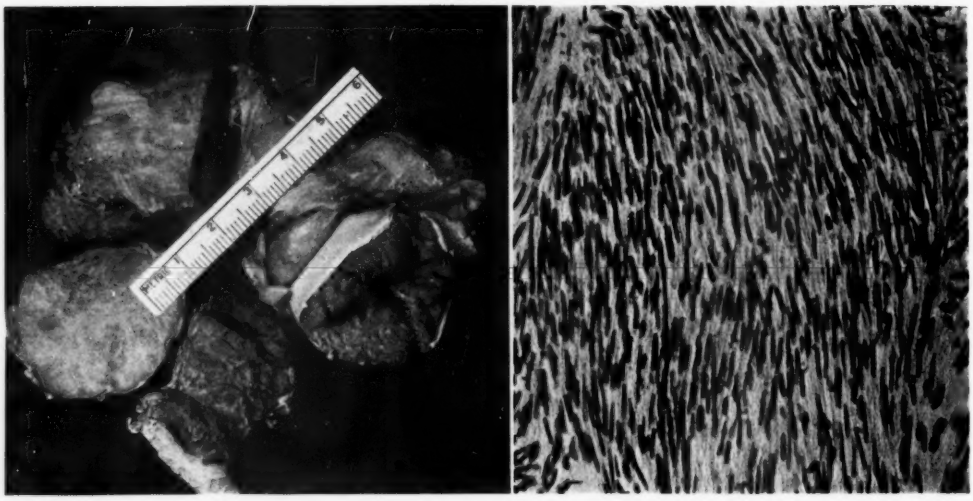

Fig. 3. a, left, Myosarcoma of the spermatic cord; b, section of same tumor; malignancy was graded 1. ×350.

didymis. Four cases have been seen at the Mayo Clinic as follows:

CASE 28. A man, aged 42 years, came to the clinic June 16, 1919, complaining of a lump on the left testis which he first had noticed 4 years previously and which had increased slowly in size. Two years before he came for examination he had had a slight pain, lasting a few days, and the week before admission pain had been noted again. On arrival here, however, it had subsided again. Examination revealed enlargement of the left epididymis to approximately 1.2 centimeters. Physical examination otherwise gave essentially negative results. A diagnosis of chronic epididymitis was made and operation advised.

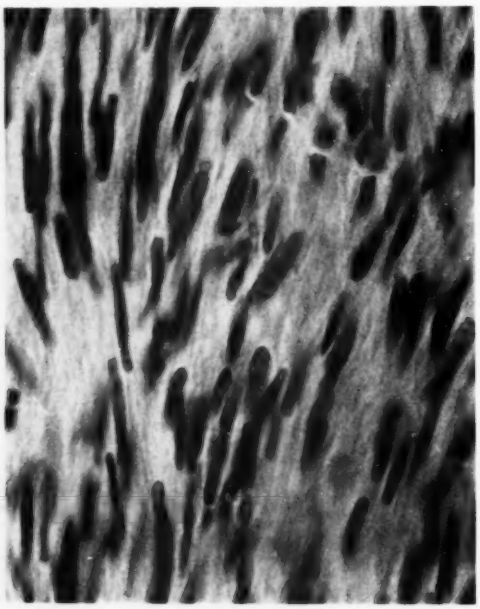

Fig. 4. Myosarcoma, grade 1. ×900.

Left epididymectomy was performed, as the left epididymis was replaced by a tumor. Then a "bottle" operation was done to prevent development of hydrocele. On gross examination, the tumor was found to measure 3 by 2 centimeters, and when sectioned it was grayish-white; the periphery of the tumor was darker than a portion in the center which was 1.5 centimeters in diameter. Microscopic examination revealed the tumor to be an angioma with marked hyperplasia of the endothelium. This central hyperplasia was the cause of the difference in color observed grossly. The low power photomicrograph (Fig. 5a) was taken at a point which includes part of the darker edge and also a portion where there was endothelial hyperplasia. The individual endothelial cells can be seen in a section of the center of the tumor (Fig. 5b). A diagnosis of angioma with endothelial hyperplasia was made. The patient was entirely well when heard from 5 years after operation.

CASE 29. A man, aged 31 years, came to the clinic February 15, 1922, complaining of a lump in the right testis which he first had noted 6 years previously. This gradually had increased in size until on admission it was approximately 1.5 centimeters

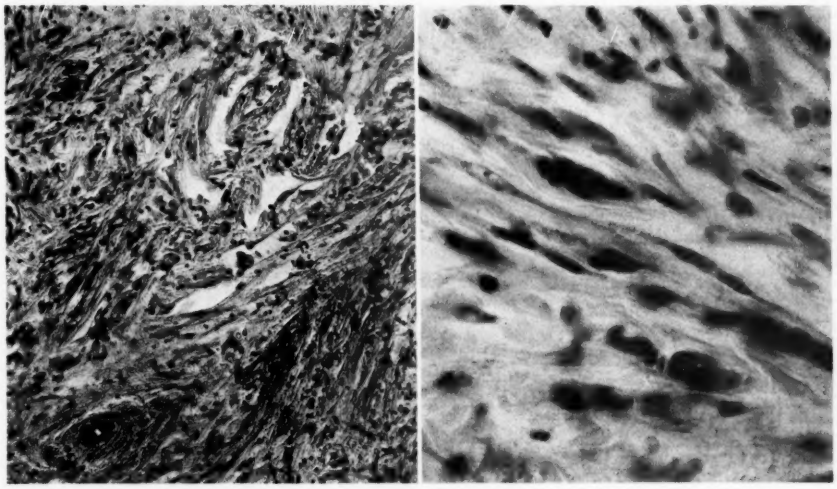

Fig. 5. a, left, Edge of tumor and endothelial hyperplasia. ×85; b, central area of same tumor, with endothelial cells. ×425.

in diameter. It had never been painful and there were no other complaints. Examination revealed an enlargement approximately 1 inch (2.5 cm.) in diameter, of firm consistence, attached to the globus major of the epididymis. Results of all other examinations were essentially negative. A diagnosis of spermatocele was made and operation was advised.

At operation a small nodule was excised from the lower pole of the right epididymis through a right, semilunar incision and Andrew's "bottle" operation was performed. The tumor measured 2 by 1.5 centimeters and on gross and microscopic examination proved to be a lymphangioma. Convalescence was entirely uneventful and the patient is well.

CASE 30. A man, aged 25 years, was first seen December 23, 1921, when he complained of epigastric distress, such as is experienced by patients who have peptic ulcer. He also complained of enlargement of the left testis which had developed after trauma 11 years ago.

On examination, the left testis was about twice normal size. Transmission of light could be demonstrated, and there seemed to be a hard mass fixed to the testis in the normal position of the epididymis. Roentgenologic examination of the stomach disclosed a duodenal ulcer. Operation for both lesions was advised.

Gastro-enterostomy was performed for the duodenal ulcer and an angioma ¾ inch (1.9 cm.) in diameter was removed from the epididymis and an Andrew's "bottle" operation for hydrocele was done. Grossly the tumor measured 2 by 1.5 centimeters and was lobulated. Microscopic section showed the tumor to be composed of hundreds of blood vessels, most of which were filled with blood. All sizes of vessels were found and the intervening stroma consisted of the same types of cells that made up the vessel walls. A diagnosis of hemangioma was made (Fig. 6).

Convalescence was uneventful and the patient was in good health in 1928 when last heard from.

CASE 31. A man, aged 44 years, had noted a swelling in the right testis for 5 to 6 years. This had been without symptoms until shortly before examination, when it had seemed to enlarge slightly and the swelling had become slightly painful. Examination revealed a small, nodular swelling in the lower pole of the right epididymis. At operation, this was found to be intimately related to the epididymis and firmly fastened to the adjacent tunica albuginea. It was 12 millimeters in diameter. Microscopic section proved the growth to be a hemangioma.

These vascular tumors of the epididymis are small. None of the tumors in the cases reported in the literature attained the size of other tumors of the epididymis. They are slow-growing, cause few symptoms, and apparently do not recur.

Hinman and Gibson stated that they were unable to find a case of dermoid cyst of the epididymis reported in the literature. Rubaschow did not mention a case, and after careful search I have concluded that there is no case of this sort on record. A patient has been operated on at the Mayo Clinic for dermoid cyst of the epididymis. The detailed report of the case follows.

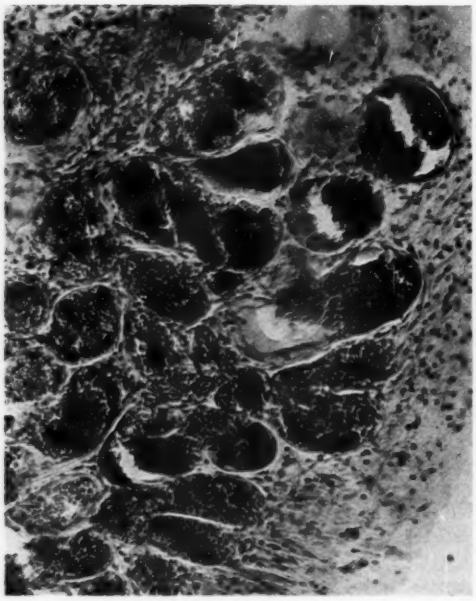

Fig. 6. Hemangioma of epididymis.

Fig. 7. Dermoid cyst of epididymis.

CASE 32. A man, aged 25 years, came to the clinic February 2, 1921, complaining of a swelling in the right groin which had been developing for the past 10 years. Four years previously, there had been a discharge of thick material from the scrotum and this had continued up to the time of admission. Occasionally there had been slight discomfort, but never any acute pain. There had not been any urinary symptoms.

Examination disclosed an enlargement of the right testis to three times normal size, with multiple sinuses in the scrotum from which a foul discharge exuded. The right ductus deferens felt nodular, and the enlargement seemed to be principally of the epididymis. Urinalysis was negative, as were all other examinations. A diagnosis of tuberculous epididymitis, with multiple sinuses, was made and operation advised.

Right epididymectomy and vasectomy were performed. The growth proved to be a dermoid cyst containing hair, a tooth and very foul, thick pus. The sinuses in the scrotum were adherent. The testis was somewhat atrophic and was not removed. The entire epididymis and a portion of the ductus deferens were excised. Gross examination of the tissue revealed it to be made up of epididymis which was cystic in portions. There were several sebaceous cysts, encapsulated by epididymal tissue. The white portion at the top of Figure 7 is a sebaceous cyst. The ductus deferens can be seen just below this, and in the lower half of the figure, a lock of hair. A fully developed tooth can be seen just to the right of the hair.

The patient's convalescence was entirely uneventful. He reported, 3 years later, that he was in excellent health.

According to the history the patient first noted beginning enlargement of the epididymis at the age of 15 years. A roentgenogram might have shown the tooth, and thus have been an aid in diagnosis, but as a dermoid cyst was not suspected, roentgenological examination was not made. This is an unusual case and apparently is the only one on record.

Calcified, degenerated hematoma of the epididymis, or calcified hydrocele, easily can be mistaken for dermoid cyst. Three such cases have been seen at the Mayo Clinic. The absence of keratin makes the diagnosis of dermoid cyst impossible.

Martin and Sermet, in 1932, reported 2 cases of cystic embryoma. These definitely seemed benign, and should be classed as such.

Malignant tumors. Ferrier and Foord, in 1934, reviewed the literature and stated that, including their own case, 15 cases of primary

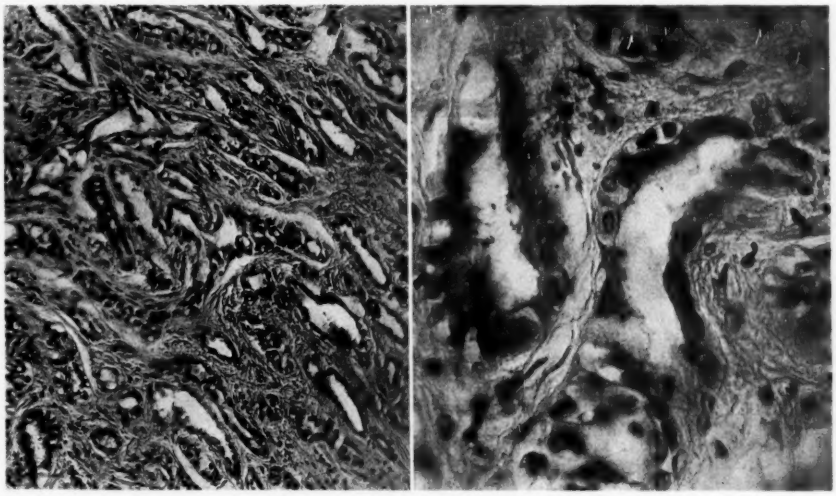

Fig. 8. a, left, Adenocarcinoma, grade 1, of epididymis. ×130; b, section of same tumor. ×425.

carcinoma of the epididymis had been reported. De Vincentiis, about the same time, described a seminoma which can be similarly classed, bringing the total number of reported cases, to date, to 16.

Seven cases of carcinoma of the epididymis have been seen at the Mayo Clinic. Of these, 5 are of relatively low grade of malignancy and two are of high grade. A description of each case follows:

CASE 33. A man, aged 56 years, came to the clinic June 27, 1916, complaining of a swelling of the left testis, which he had noted for 6 years. Recently the tumor had begun to increase in size to a noticeable degree. There was also a slightly painful swelling in the right testis which had been present for 15 years.

Examination disclosed a fluctuating, painless swelling around the left testis, which transmitted light, and a similar although smaller swelling around the right testis. A diagnosis of bilateral hydrocele was made.

Andrew's "bottle" operation was performed for bilateral hydrocele of moderate size and a small tumor of the lower pole of the right epididymis was found and excised. On gross examination this tumor was bluish white in color and apparently was well encapsulated. It was 7 millimeters in diameter. Microscopic section of the tumor revealed a rather interesting structure. Numerous acini lined with epithelial cells could be seen in the low power field (Fig. 8a). Most of the cells were well differentiated but some of them had rather large nuclei which contained large nucleoli. Since the tumor appeared to be fairly well differentiated it was diagnosed adenocarcinoma grade 1. It was a relatively benign tumor, but, nevertheless, an adenocarcinoma. A photomicrograph of higher power is shown in Figure 8b.

The patient had an uneventful convalescence and is well.

CASE 34. A man, aged 27 years, came to the clinic September 3, 1918, stating that 7 years previously he first had noted slight enlargement of the right testis, and this slowly had increased in size. One year previously a dull, intermittent pain in the testis had begun. There were no other complaints. On examination a firm swelling, about 2.5 centimeters in diameter, was found in the lower pole of the right epididymis. Roentgenograms of the chest and bones, and the reports received on all other examinations were negative. A diagnosis of tuberculous epididymitis was made.

Partial epididymectomy was performed and a tumor about 1 inch (2.5 cm.) in diameter was removed from the lower pole of the epididymis. On gross examination the tumor, represented in Figure 9a, was firm, although not nearly as firm as a fibroma and was well encapsulated. It had the appearance of malignant tissue. Microscopic examination of the tissue disclosed it to be adenomatous in structure, and that rather loose, fibrous, interstitial tissue was present. The glands were lined with definite epithelial cells, some of which were rather broad. A close resemblance to mixed tumor was noted. Figure 9b is a low power photomicrograph of a typical section of the tumor.

The patient's convalescence was uneventful. He returned home and on recent inquiry stated that there has been no recurrence and that he is in good health.

CASE 35. A man, aged 30 years, came to the clinic June 13, 1929, complaining of stomach trouble for the past 3 years. He also had noted a nodule in the lower pole of the left epididymis for 10 years. In that time the growth had been so slow that he could scarcely detect any change in size from year to year. There was no history of gonorrhea.

Examination disclosed a firm nodule, measuring 2 by 2 centimeters, situated in the lower pole of the left epididymis. All other examinations were negative, including roentgenograms of the chest and bones. The stomach was found to be normal; the distress of which he complained was caused by constipation. A diagnosis of tumor of the testis was made and operation was advised.

At operation the testis was delivered through a left inguinal incision. The tunica vaginalis was incised, and a tumor of the epididymis was removed. As it appeared to be of a low grade of malignancy grossly, the testis was preserved. The tumor was grayish-white, firm, well encapsulated, and measured approximately 2 centimeters in diameter. On microscopic section this tumor was found to be adenomatous in structure and it closely resembled the tumor removed in Case 34. This tumor, as in the other case, was an adenocarcinoma grade 1.

The patient made an uneventful convalescence. He was given roentgen irradiation over both groins before his dismissal July 11, 1929, at which time the wound was healed and he was feeling well.

CASE 36. A man, aged 38 years, came to the clinic December 13, 1912, complaining of a swelling in the left testis which had appeared 3½ years previously and had gradually enlarged. One year before admission there had been an attack of acute pain in the testis which had been referred to the left groin. There were no other symptoms.

Examination revealed the left testis to be enlarged four times normal size. The tumor seemed to be principally in the epididymis, which was hard and nodular. Operation was advised.

The left testis and a portion of ductus deferens were removed at operation as the neoplasm apparently involved principally the epididymis. Gross examination of the tumor disclosed involvement of the epididymis in its entire extent. The tumor was white, solid looking, and moderately firm. The size was approximately that of the testis (Fig. 10). There was slight involvement of the testis, apparently by direct extension. On microscopic section the tumor was found to be a carcinoma of a high grade of malignancy with little differentiation of cells. Typical photomicrographs are represented in Figure 11a and b.

As letters of inquiry have been returned unclaimed, the probabilities are that the patient is dead.

CASE 37. A man, aged 53 years, came to the clinic January 30, 1928, complaining of a swelling of the right testis which he had first noted 2 months previously. He also complained of chronic colitis. There were no symptoms of other abnormal conditions.

Examination revealed the right testis to be enlarged to approximately the size of a lemon (about 7 cm. long). Light was readily transmitted, but because of the rather firm consistence of the swelling a diagnosis of tumor of the testis was made and operation was advised.

At operation a tumor involving the right epididymis was found and removal of the entire right testis seemed advisable and was done. Gross examination revealed the tumor to be firm and yellowish-white. It arose in the epididymis and encircled the greater portion of the testis but did not extend into it. The ductus deferens ended in the tumor tissue (Fig. 12). Microscopic examination of the tumor disclosed it to be a carcinoma of a high grade of malignancy. There was practically no differentiation of the cells, which were closely packed and practically filled by the large nuclei; very little cytoplasm was visible. Most of the cells contained large nucleoli (Fig. 13 a and b).

The postoperative course was uneventful. The patient was re-examined 1 year later and there was no evidence of recurrence or of metastasis.

CASE 38. A man, aged 29 years, came to the clinic in September, 1933, complaining of pain in the region of the right testis. Examination disclosed a hard, discrete nodule which was thought to be the end-result of chronic epididymitis. Since the patient seemed to be incapacitated, epididymectomy was advised and performed. The nodule seemed definitely discrete and was easily excised from the lower pole of the epididymis. Since on microscopic examination

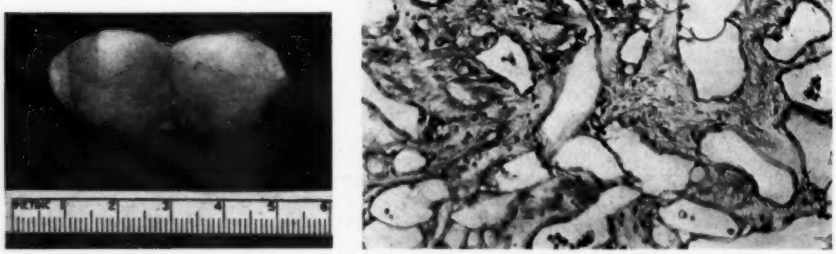

Fig. 9. a, left, Adenocarcinoma of epididymis; b, section of same tumor; malignancy was graded 1. ×120.

it was the pathologist's opinion that the tumor was an adenocarcinoma, grade 1, right castration was performed. Careful examination of the testis and its coverings disclosed nothing abnormal.

CASE 39. A man, aged 54 years, complained that 4 years prior to admission he had injured the right testis when he had fallen astride a gate. A small hard lump developed and had been present ever since. Operation was advised and performed July 12, 1934, at which time the nodule, 1 centimeter in diameter, was found in the lower pole of the epididymis. Frozen section proved it to be an adenocarcinoma; hence right castration was performed. Further microscopic study of the tumor resulted in a diagnosis of adenocarcinoma, grade 2, arising in the epididymis; the testis and coverings were normal. Deep roentgen therapy was given in the usual manner; 6 months later the patient reported excellent health.

Fig. 10. Carcinoma of the epididymis.

Ten cases of sarcoma of the epididymis, which are well described and seem authentic, have been reported in the literature, all prior to 1904. One of them a boy aged 15 years, in whom a tumor of the left epididymis developed after trauma, castration, and removal of the femoral lymph nodes, resulted in cure. The other cases all simulated cases of tumor of the testis in their clinical course.

Teratoma is an extremely rare tumor of the epididymis. Barringer reported the only case but he did not state definitely that castration was performed to prove the nature of the growth. Exploratory abdominal incision was made and radium treatment given. No description of the tumor is published with the case report. Hinman and Gibson reported a case which they referred to as a seminoma of Chevassu. From the description and photomicrographs, the classification of it as carcinoma seems best. It was so classed in Ferrier and Foord's review. This would leave Barringer's case as the only one of teratoma.

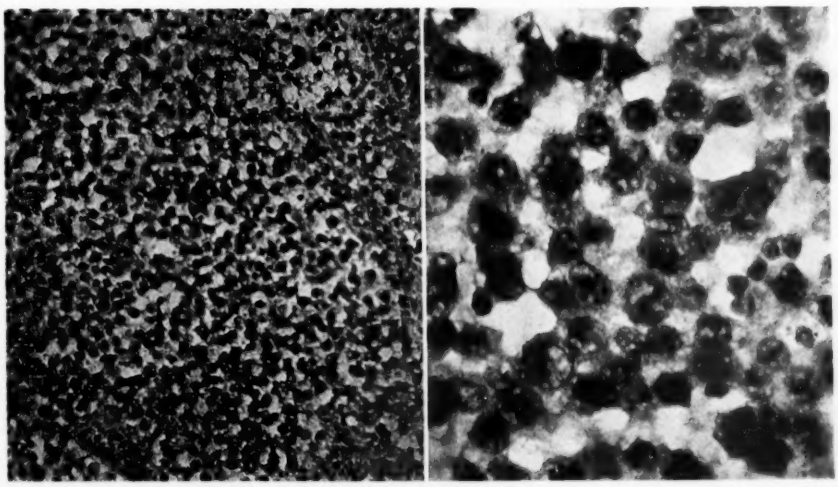

Fig. 11. a, left, Section of same tumor as that represented in Figure 10, carcinoma, graded 4. ×130; b, section of same tumor. ×600.

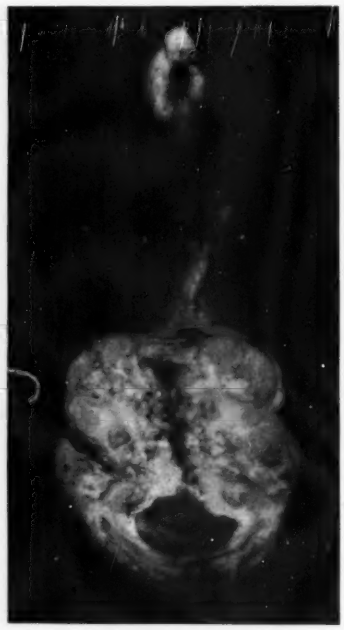

Fig. 12. Carcinoma of epididymis.

Comment. From the review of the literature and from the foregoing cases tumors of the epididymis seem to occur in the proportion of 40 per cent benign to 60 per cent malignant. Of the 25 benign tumors 2 were adenomas, 1 was a lipoma, 8 were myomas, 8 angiomas, 3 fibromas, 1 was a cystic dermoid and 2 were cystic embryomas. Of the 36 malignant tumors 23 were of epithelial origin, 12 of sarcomatous type, and 1 was a teratoma. The fact that about 40 per cent of these tumors of the epididymis are benign should be kept in mind in considering cases of tumor of the testis, or what seem to be tumors of the testis. The possibilities of a favorable prognosis following surgical exploration of what appears to be a testicular tumor should justify the urging of operation in all such cases unless metastasis to other parts of the body can be demonstrated.

TUMORS OF THE TUNICA VAGINALIS

The tunica vaginalis is of far more importance than the tunica albuginea in regard to formation of tumor. It is often very difficult and sometimes practically impossible, to distinguish tumors of the tunica vaginalis from those arising in adjacent structures. For this reason, varying opinions as to the frequency of occurrence of these tumors have been expressed. A tumor thought by an observer to arise from the tunica vaginalis may, on review by another, be classified as a tumor of the spermatic cord. From the review to follow, it can be seen that the majority of the tumors are benign and that the total number reported in the literature is approximately 50.

Benign tumors. Only 3 authentic cases of lipoma have been reported in the literature. Park, in 1886, removed a lipoma weighing 3 pounds (1.4 kg.) from the right tunica vaginalis. The tumor was supplied with blood vessels from both the testis and spermatic cord and there were numerous fibrous trabeculæ projecting from the testis out into the fatty mass. Placiteli and Deming, in 1933, each reported a case of lipoma of the tunica vaginalis. In the latter's case, the lipomas were bilateral and quite small.

Hinman and Gibson stated that only 2 cases of adenoma have been reported in the literature, that by Muhsam, in 1898, and that by Nicolopoulo, in 1895. A case which I believe should be classified as an adenoma follows:

CASE 40. A man, aged 60 years, came to the clinic August 5, 1930, stating that he had suffered with a hydrocele for many years. This had been aspirated on many occasions without incident, but 3 weeks prior to admission, a few days after aspiration had been performed, the scrotum had begun to swell rapidly and had become sensitive. There were no signs of inflammation. On examination, a rounded mass, about 7.5 centimeters in diameter, was found in the right side of the scrotum; with this exception the patient was in excellent physical condition. Exploration was advised. At operation, a thick walled hydrocele was opened readily, disclosing a cystic mass intimately attached to the parietal leaf of a thickened tunica vaginalis, just opposite the upper pole of the testis and the upper portion of the epididymis. It was definitely encapsulated and was enucleated readily. The thickened tunica vaginalis was cut away and the edges sutured to control oozing.

The mass weighed 150 grams and measured 9 by 6 by 5 centimeters. The cut surface of the tumor, on gross inspection, presented an appearance somewhat similar to that of an adenoma of the thyroid gland.

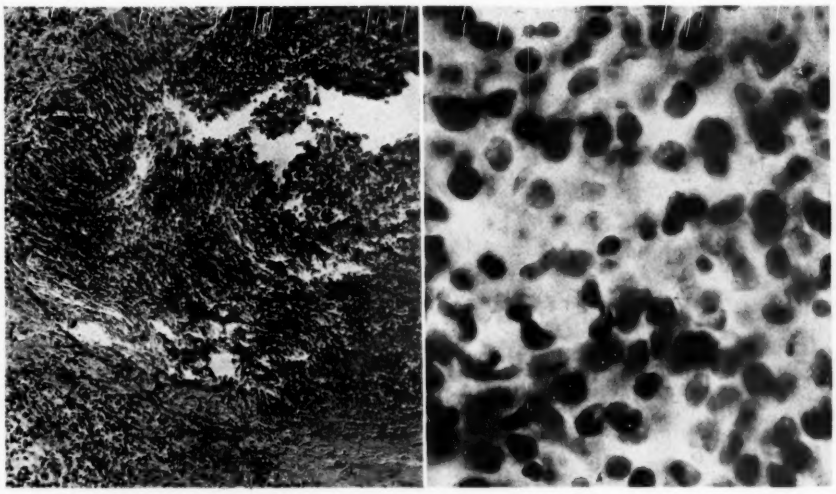

Fig. 13. a, left, Carcinoma, grade 4, section of same tumor as that represented in Figure 12 ×65; b, section of same tumor. ×600.

It was more spongy in structure and the glandular portions contained a clear fluid, except in one part, in which the fluid was hemorrhagic. This part might have been punctured by the needle when the hydrocele was aspirated. The pathologist's report of the microscopic study of sections cut from the growth was hemorrhagic cystadenoma. Convalescence was uneventful.

Five cases of myoma have been reported in all of which the tumors probably had their origin in the gubernaculum.

Of the vascular tumors, Rindone, in 1901, reported a tumor originating in the tunica vaginalis, which he regarded as lymphangioendothelioma. Similar cases have been recorded by Micotti in 1926, and by Scarpello, in 1927. Nora, in 1933, described an endothelioma.

Rubaschow (36), in 1926, collected from the literature reports of 16 cases of fibroma, which he was certain were tumors of the tunica vaginalis. Since that time, Stricker and Franck have reported a case in which the tumors were multiple. Oehlecker, in 1930, reported a case of a man, aged 26 years, in which the tumor was found to be situated in the parietal leaf of the tunica vaginalis just above the upper pole of the testis, and to extend downward, pressing on the testis. While it might be considered as a tumor of the spermatic cord, it seems best to classify it as arising in the testicular tunic.

A case of fibroma of the tunica vaginalis which came to operation at the clinic is described next.

Case 41. A man, aged 45 years, came to the clinic November 16, 1915, stating that he recently had noticed a small nodule in the right testis. There had been no symptoms from this enlargement. On examination, a nodule was found in the right epididymis or very closely adjacent to it. It was firm, not tender, and approximately 1.5 centimeters in diameter. All other examinations were essentially negative including roentgenograms of the chest. A diagnosis of chronic epididymitis, which possibly might be tuberculous, was made and operation advised.

Right epididymectomy performed, removing the ductus deferens up to internal ring. As a small hydrocele was present, corrective operation was done.

The tumor, on gross examination, had the appearance of a fibroid and was well encapsulated. It arose intimately from the dense, inelastic fibrous tissue surrounding the epididymis and was attached to it. The tumor did not encroach on the tubules making up the epididymis and could be pulled away from the body of that organ. The fibrous tissue investing the epididymis was very tough and inelastic and was apparently the visceral layer of the tunica vaginalis, normally found there. From this the tumor was sharply demarcated and yet was densely adherent to it. A capsule separated the tumor from the epididymis (Fig. 14a). Microscopic section revealed the growth to be a typical fibroma (Fig. 14b). The patient made an uneventful convalescence.

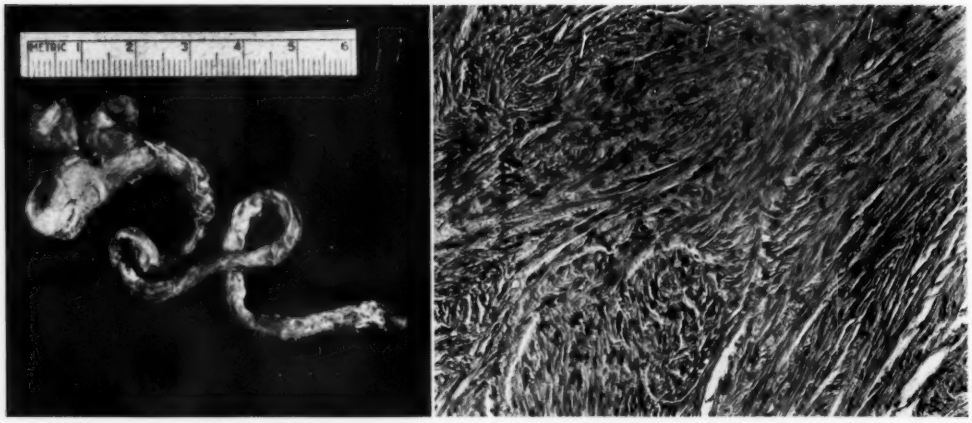

Fig. 14. a, left, Fibroma of the tunica vaginalis; b, section of the same tumor. ×140.

Malignant tumors. Rubaschow (36) collected reports of 15 cases of sarcoma of the tunica vaginalis and to these the only cases to be added are those of Valdoni, who reported a case of sarcoma of a patient 17 years of age, and of Donati who, in 1934, reported a case of fibrosarcoma. Rubaschow (36) called attention to the fact that the majority of the tumors occur in very young individuals. Valdoni's patient was only 17 years old and, in the 11 cases listed by Rubaschow (36), the oldest patient was only 35 years of age. Sarcoma of the testicular tunics is in this respect similar to that of the testis. On the other hand, sarcoma of the spermatic cord rarely occurs in young individuals.

TUMORS OF THE TUNICA ALBUGINEA

Only 4 cases of tumor of the tunica albuginea have been recorded in the literature. They were included in the review of Hinman and Gibson. In all of the cases the tumors proved to be fibromas. The operation employed was castration in three of the cases, and in the other, enucleation of the tumor, which was small and well encapsulated, was possible.

CLINICAL DIFFERENTIATION OF TUMORS

Because of their rarity tumors of the structures considered in this paper are scarcely ever considered in the differential diagnosis of intrascrotal enlargements. In any given case tumor of the testis should be considered first. If, however, the testis is found to be separate from the growth on palpation, the interest lies in distinguishing the extratesticular scrotal tumors as a whole from the so called pseudotumors, such as hematocele and spermatocele. One should also think of tuberculous epididymitis, traumatic orchitis with associated hydrocele or hematocele, and acute hydrocele with torsion of the cord. Lipomas of the cord are often confused with inguinal hernia. The fact that these tumors, often benign, simulate malignant tumors of the testis seems to be the chief point of interest.

TREATMENT

In all cases surgical exploration is the procedure of choice. Since a large percentage of tumors of the epididymis, spermatic cord, and testicular tunics are benign, it is often possible to do a conservative operation. Castration should not be performed until sections of the tissue have been studied under the microscope.

If the tumor is found to be malignant, local removal, that is, castration, followed by treatment with roentgen-rays or radium, seems to be all that is indicated. The results of the so called radical operation, involving removal of retroperitoneal lymph tissue, do not justify its use.

SUMMARY AND CONCLUSIONS

Tumors of the epididymis, spermatic cord, and testicular tunics are extremely rare. Twenty-six cases of tumor of the spermatic cord seen at the Mayo Clinic are reported; of these tumors, 21 were lipomas, 1 was a fibroma, 1 a hemangioma, 1 a cystadenoma, 1 a fibrosarcoma, and 1 a myosarcoma.

Thirteen cases of tumor of the epididymis seen at the Mayo Clinic are reported. Among these tumors there was one dermoid cyst, a hitherto unreported type of epididymal enlargement, 1 cystadenoma, 4 angiomas, and 7 carcinomas. Of the 7 malignant tumors 4 were adenocarcinomas, grade 1, 1 a carcinoma, grade 2, and 2 carcinomas, grade 4.

Two cases of tumors arising in the tunica vaginalis are reported, 1 of the tumors was a fibroma and the other a cystadenoma.

The following conclusions may be drawn:

1. Approximately 70 per cent of all tumors of the spermatic cord are benign.

2. Approximately 40 per cent of tumors of the epididymis are benign.

3. Approximately 60 per cent of tumors of the testicular tunics are benign.

4. The prognosis is more favorable in cases of tumor of the spermatic cord, epididymis and testicular tunics than in cases in which tumor originates in the testis; tumors of the testis are, almost without exception, highly malignant.

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CLINICAL SURGERY

FROM THE MEMORIAL HOSPITAL

GASTROSTOMY IN THE MANAGEMENT OF GASTRIC AND ESOPHAGEAL CARCINOMA

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SEDILLOT, in 1849, was the first surgeon to attempt the formation of a permanent gastric fistula in the treatment of cancer of the esophagus and he gave to the procedure its present name—gastrostomy. Twenty-six years later the first successful operation was performed, and since then many different types of gastrostomy have been proposed and described in the literature. The usefulness of this operation has increased with the improvement in the type of procedure employed and with the general improvement in surgical technique.

The ideal gastrostomy should provide a gastric fistula not affected by the action of gastric juices. It must be continent and permit no leakage of gastric juices or ingesta. It must also be permanent and so fashioned as to permit the patient easily to insert his own catheter for each feeding. The stoma must be readily dilatable so as to allow repeated instrumentation through it, such as gastroscopy, retrograde esophagoscopy, and bougienage. It is desirable that the operation lend itself well to local anesthesia. There should be no operative shock, and the procedure should be possible in the contracted stomach (due to disuse or disease located in the cardia).

The satisfactory gastrostomy must permit gastric digestion immediately and must not confine the patient to bed continuously more than 2 or 3 days after operation. Of all the types so far devised the Janeway (1 and 3) gastrostomy most nearly fulfils the above requirements. On the head and neck service at the Memorial Hospital this type of gastrostomy has become a common preliminary step in the treatment of carcinoma of the esophagus and cardia of stomach. Since 1928 this operation has been carried out in 163 cases.

OPERATIVE TECHNIQUE

Under local infiltration of the skin with 1 per cent novocain containing 10 drops of adrenalin to the ounce, together with intercostal nerve block of plain 1 per cent novocain, a longitudinal incision is made over the outer third of the upper left rectus muscle from the costal margin downward for not more than 6 centimeters. The outer rectus fascia is incised and the rectus muscle split in the direction of its fibers. The fibers of the transversalis muscle are incised in the direction of the incision and peritoneum infiltrated with 1 per cent novocain and opened.

A brief and necessarily limited exploration of the anterior surface of the liver and the pre-aortic and perigastric regions for secondary deposits is carried out. The anterior wall of the body of the stomach is usually found directly beneath the incision, but in thin patients with elongated, flattened chests and in patients with cancer of the cardiac portion the stomach may be situated rather high, but with slow gentle traction it has always been possible to deliver a sufficient portion of the anterior stomach wall into the wound. Five Allis clamps are then applied outlining a rectangular flap 2 centimeters wide and 3 centimeters in length with its base directed toward the greater curvature, shown in Figure 1. The wound edges are carefully protected with small, thin, laparotomy pads, the outlined flap is quickly incised, and all bleeders are clamped and securely ligated. The stomach may be found much contracted, particularly in its transverse dimensions, and, if so, it will stretch markedly; this fact should be borne in mind when the flap is outlined.

The closure of the defect is begun at the middle of the incision parallel with the lesser curvature, and is continued up along the edges of the flap to form a gooseneck tube. A running suture of No. 00 chromic catgut is used for this mucosal layer, and before it is entirely closed a No. 12 French catheter is inserted into the stomach. A running interlocked Lembert suture of No. 00 chromic catgut is used to close the serosa. The stomach

[1] From the Head and Neck Department of Memorial Hospital, service of Dr. Hayes E. Martin.

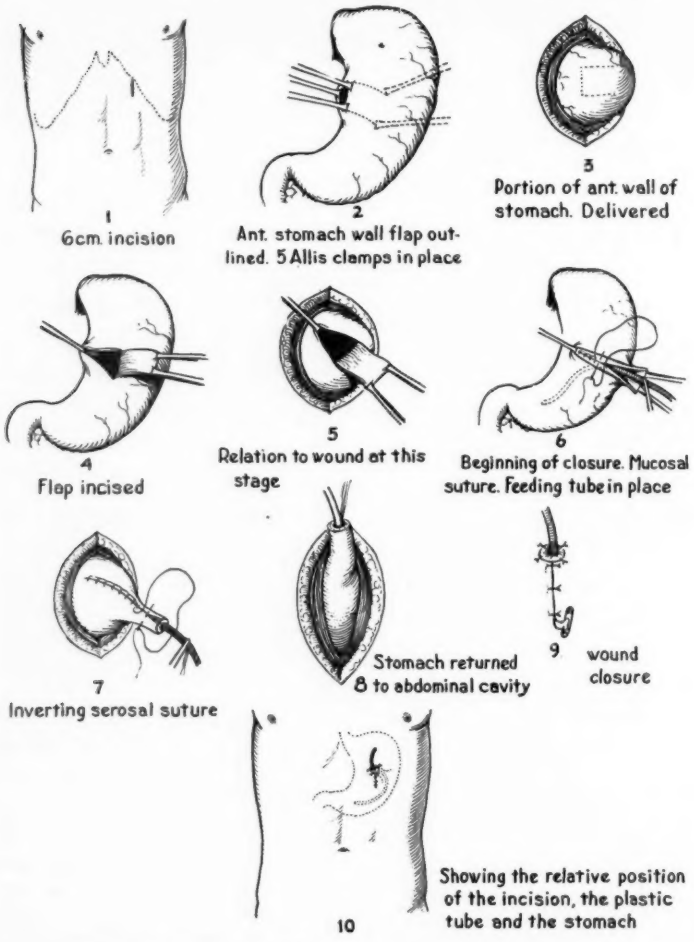

Fig. 1. Janeway gastrostomy: 1, Incision. 2, Outlining of rectangular flap of anterior stomach wall—first incision parallel with lesser curvature. 3, The anterior stomach wall has been drawn into the wound to prevent peritoneal contamination when the stomach is opened. 4, Rectangular stomach wall flap incised. 5, Relation of stomach to wound at this stage. 6, Mucosa partly closed and a No. 12 French catheter inserted. 7, A running interlocked Lembert suture of No. 00 chromic catgut closes the serosa. 8, Gooseneck tube brought out through upper angle of wound. 9, Mucosa sutured to skin edge and abdominal wound closed. 10, Relationship of stoma to stomach and anterior abdominal wall.

is then returned to the abdominal cavity, the operator and assistants change into fresh sterile gloves and the wound is closed in layers. An assistant holds the gooseneck tube with the suture line in contact with the upper wound angle. No. 1 plain catgut interrupted sutures are used for the peritoneum and transversalis muscle. One loosely tied mattress suture of the same suture material is used to approximate the cut edges of the rectus muscle loosely over a small wick of iodoform gauze which is brought out through the lower angle of the wound. The anterior rectus fascia is closed with interrupted No. 2 chromic catgut sutures and the posterior surface of the

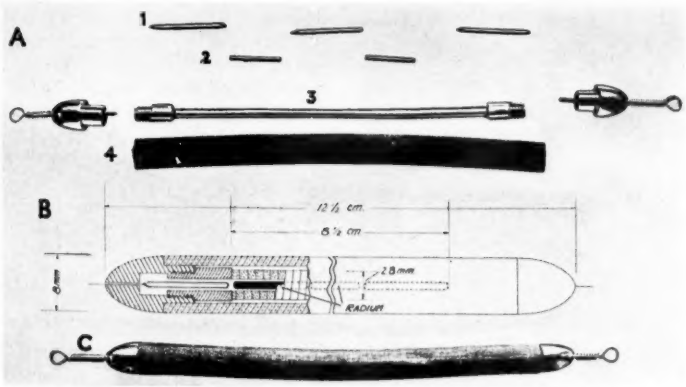

Fig. 2. The esophageal radium element tandem. A, Unassembled: *1*, Three radium element tubes of 10 milligrams each. *2*, Two dummy tubes. *3*, Flat wire stainless steel tubing with nickel steel end pieces. *4*, Black rubber tubing. B, Mechanical drawing of tandem. C, Tandem assembled ready for use.

gooseneck tube is anchored to this fascia by one suture of No. 00 chromic catgut which passes through the serosal coat only. The skin is closed with three interrupted, vertical, mattress sutures of medium dermal and the mucosa of the gooseneck stoma is fixed to the skin of the upper wound angle by four interrupted black silk sutures. A dry dressing is applied and the feeding tube is fixed to the dressing in such a manner as to prevent it being accidentally withdrawn from the stomach.

It is obvious that this operative procedure requires a little more surgical care and skill than is necessary in the simpler forms of gastrostomy, but this possible objection is outweighed by the more satisfactory postoperative results of the Janeway operation.

The iodoform gauze drain is removed in 24 hours, the patient is out of bed on the second or third postoperative day, and the sutures are removed on the fifth postoperative day. The postoperative care has been reported in the recent past (5) and will not be repeated here. After 7 days the gooseneck tube is healed firmly and will permit gentle instrumentation through the stoma, and intra-esophageal radiation with the radium element tandem may be started without interfering in the least with the patient's nutrition.

If gastrostomy is delayed until late in the course of the patient's disease then a definite, rather high, postoperative mortality must be expected, for a certain number of these patients are going to die of their disease within the period of postoperative convalescence. Our previously reported (2) operative mortality of 5.8 per cent is the lowest recorded for gastrostomy and each fatality in our series was due to the patient's disease and not to the operative procedure.

In order to maintain low morbidity and operative mortality rates, it has been learned from experience that certain factors must be observed. The operation must be done under local anesthesia as general anesthesia in these elderly, dehydrated, and emaciated patients is hazardous and unnecessary. The abdominal incision is limited to 6 centimeters because this will permit adequate exposure and at the same time minimize the danger of postoperative wound infection which, if it does occur, will be a small matter rather than one of serious import. Postoperative evisceration does not occur, and a small incision allows the patient to be out of bed safely on the second or third postoperative day. The short incision will limit abdominal exploration, but this in turn will lessen postoperative reaction.

From other clinics where the Janeway gastrostomy is being performed, there have come personal reports of sloughing of the terminal portion of the gooseneck tube. There are three causes of this complication: (1) The flap of anterior stomach wall is cut too long or too narrow or at right angles to its blood supply, which should come from the vessels of the greater curvature. (2) The anterior fascia of the rectus muscle is sutured too snugly about the gooseneck tube and postoperative edema causes strangulation. (3) The one suture used to anchor the tube to the anterior rectus fascia is placed too deeply and shuts off the arterial supply to the terminal portion of the plastic tube.

Fig. 3. An olive tipped bougie, *A*, has been introduced into the stomach and after the gastrostomy stoma has been dilated, a small esophagoscope is inserted into the stomach and the bougie is picked up.

The stoma should be small and a small catheter (No. 12 French) should be used for feedings, as a larger tube will dilate the opening and permit leakage.

The value of gastrostomy in the treatment of gastric and esophageal cancer will depend largely on the care and skill with which the operation is carried out. A satisfactory gastrostomy is a very necessary preliminary step in the treatment measures to be described.

THE INTRA-ESOPHAGEAL RADIUM TANDEM

The tandem (Fig. 2) we are using at present is a moderately flexible rubber covered applicator of flat, coiled, stainless spring steel gilly wire with smooth blunt nickel steel ends each with a loop of stainless steel wire to facilitate attachment of the shoemaker's twine used in manipulating and holding the tandem in its proper position in the esophagus. It has an overall length of 12.5 centimeters although it is well to have a second and shorter applicator for the treatment of small lesions and those just below the level of the cricopharyngeal constriction. The radiation is produced by three radium element needles each of 10 milligrams' strength. These needles have a filter of 0.25 millimeter of platinum and the total filtration of the applicator is equivalent to 0.4 millimeter of platinum. The radiation is 98 per cent γ and 2 per cent hard β.

Radon is not as satisfactory as the element because its radiation value would vary considerably over a 24 hour treatment period and frequent replacements would be necessary, thus leading to inadvisable handling and exposure by the clinicians and technicians. It is possible to vary the position of the radium needles in the container and so concentrate the dose by the use of two dummy needles as shown in Figure 2, A.

The stainless steel tube of flat gilly wire is flexible enough to allow the tandem to be readily drawn through the gastrostomy stoma and past the angle at the junction of stomach and esophagus. Its flexibility also facilitates its peroral extraction. The flat wire allows even radium filtration not possible when a round wire is used. This tubing is safe and is easily cleaned and does not rust and cause difficulty in the removal of the radium needles. The inside diameter of this tube is 1.5 millimeters—sufficient to allow easy introduction of the radium element needles. The outside diameter is 8 millimeters.

Securely screwed to each end of the flat wire tube is a smooth, blunt nosed, nickel silver piece which allows easy introduction without trauma through the gastrostomy stoma and also through the narrowed, diseased portion of the esophagus. Anchored in each of these end pieces is a short, nickel silver wire with a terminal loop to which is attached the strong twine used in manipulating the tandem. A section of ordinary black rubber tubing 8 millimeters in its outside diameter covers the flexible metal portions of the tandem.

The tandem is placed accurately in the esophagus at the level of the growth by combined gastroscopy and esophagoscopy. If the growth will permit the passage of a small (7 millimeter) olive tipped bougie, this is done under direct vision; otherwise the patient is given a black silk thread to swallow at the rate of a foot per hour for 24 hours. The gastrostomy stoma is gradually dilated with graduated Hegar cervix dilators and a small 9 millimeter esophagoscope is passed into the stomach, the gastric contents is aspirated, the organ is distended with air, and the olive tipped bougie or string is picked up with biopsy forceps and brought out through the stoma (Fig. 3). Stout shoemaker's twine is substituted for the silk and tied to the tandem which is then passed through the gastrostomy stoma into the stomach and drawn upward into the esophagus to the lower level of the growth. The oral end of the string is then passed through a regular adult esophagoscope which in turn is inserted into the esophagus down to the tumor. By steady traction on the oral end of the string, the tandem is pulled upward under direct vision until its proximal end is 3 centimeters above the upper limits of the disease (Fig. 4).

The esophageal lumen is usually quite narrow, and the tandem tends to be held firmly in position

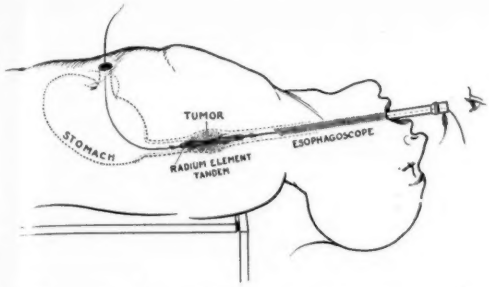

Fig. 4. The radium element tandem is pulled upward by steady traction until, under direct esophagoscopic vision, the level of the esophageal lesion is reached.

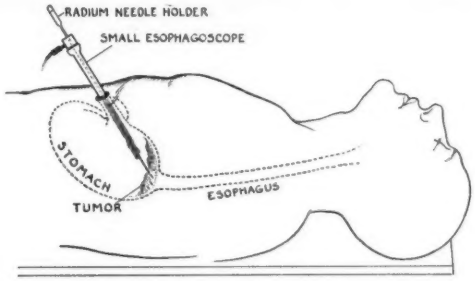

Fig. 5. The method of inserting gold filtered radon seeds into a cancer of the cardiac portion of stomach by means of an esophagoscope inserted through the gastrostomy stoma.

by the stricture, but it is nevertheless anchored in place by fastening the proximal end of string to a tooth and the distal end with adhesive tape to the anterior abdominal wall. The length of the proximal and distal strings is measured and these measurements are used in reinserting the tandem for the next treatment, thus eliminating the necessity for repeated endoscopic procedures. The tandem is left in position for 24 hours during which time the patient expectorates his saliva and regular nutrition is maintained by gastrostomy feedings.

At the end of 24 hours, when a dose of 720 milligram hours (30 milligrams for 24 hours) has been delivered, the tandem is drawn upward and out through the mouth, a fresh length of string having been tied to the distal end and drawn through the stoma to be used in reinserting the applicator for the next treatment.

The tandem is inserted every 2 days over a period of 8 to 12 days, during which time a total of from 2,280 milligram hours to 4,320 milligram hours is delivered to the tumor area. The patients do not complain of discomfort during treatments, and if the throat is well cocainized and 1 per cent novocain is used to infiltrate the skin about the stoma before dilating it, they do not greatly mind the original endoscopic procedure and initial insertion of the tandem.

Gastrostomy serves no useful purpose in cancers of the pyloric end and body of stomach, but it is of value in the inoperable lesions located in the cardiac portions of the stomach. Growths in this latter region are apt to be difficult to diagnose roentgenographically, and on peroral endoscopy it may be impossible to visualize the growth or remove a biopsy. In such instances the Janeway operation permits inspection of the growth and allows the operator to remove a specimen for microscopic diagnosis, at the same time he may measure the lesion accurately, estimate and insert the dose of gold filtered radon seeds necessary to control the growth (Fig. 5). By weekly gastroscopy through the gastrostomy stoma the radium reaction may be followed and if regression is incomplete, check-up biopsies may be taken and more radon seeds added as necessary.

If an esophageal lesion is to be treated by inserting radon seeds, it has been found a simple task with the aid of the esophagoscope to insert the radon seeds accurately into the upper two-thirds of the lesion, but, to plant gold seeds satisfactorily in the distal third of the growth, it is necessary to visualize this portion of tumor by retrograde esophagoscopy through the gastrostomy stoma. For routine work in the esophagus and cardia of stomach, gold filtered radon seeds ranging in strength between 1.25 millicuries to 1.50 millicuries each have been found most satisfactory.

Patients with cancer of the esophagus come to us at a late stage in their disease. They are often quite emaciated and dehydrated, their tumors are large, ulcerated, and infected and frequently cause complete obstruction of the lumen (6). Many of these growths will shrink away and the esophageal lumens will open up under the divided dose method of treatment by external irradiation. However, the beneficial effects of the radiation come on slowly—20 to 30 days after commencing treatment and, during this interval, the esophageal lumen is apt to become completely stenosed due either to esophagitis, continued growth of tumor, or the early initial hyperemic effect of the X-radiation. In these cases it is necessary to do a gastrostomy before X-radiation is started, so that the treatment sequence will not be interrupted. Later, when the tumor has re-

gressed and the esophagitis has lessened, as it practically always will under external radiation, it is often possible to use the radium element tandem which previously could not have been inserted without excessive trauma to the growth.

If an esophagectomy is planned, a preliminary gastrostomy should be carried out as the first step in the procedure and the Janeway type is here again most satisfactory for, although much is written about the formation of a new anterior subcutaneous esophagus from loops of bowel, etc., we have not seen or heard of a case in which such a procedure was productive of a satisfactory result and the "rubber esophagus" of Torek and Eggers when connected to a Janeway gastrostomy is still the most practical substitute for the normal viscus.

Finally, there is the occasional case which comes to us too late to warrant aggressive therapy yet the patient is aware of his prognosis and wishes for purposes of business, etc., to carry on as long as possible. In this group gastrostomy alone will prolong life and prevent death by starvation.

SUMMARY

In cancer of the esophagus and cardiac end of stomach, if a gastrostomy is to be done, the Janeway type of operation is indicated because it possesses the following advantages:

1. It allows the instrumentation necessary for the accurate implantation of gold seeds in the lowermost portion of an esophageal cancer and allows the safe retrograde insertion of the radium element tandem in the esophageal lumen at the site of the tumor.

2. At operation or through the resulting stoma, it is possible to obtain a biopsy from a lesion located in the cardiac portion of the stomach and to insert gold seeds into it under direct vision and also to watch the ensuing radium reaction.

(3) Retrograde bougienage for the dilating of a post-treatment fibrotic esophageal stenosis may be safely carried out with graduated rubber dilators drawn through the mucosa lined stoma.

A gastrostomy is often necessary as a safety factor in cases of carcinoma of the esophagus selected for a course of X-radiation by the divided dose method.

The operative technique of the Janeway gastrostomy is described in detail and a satisfactory radium element tandem for intra-esophageal irradiation is described together with the technique of its use.

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PATHOLOGICAL FRACTURES DUE TO MALIGNANT DISEASE

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PATHOLOGICAL fractures due to malignant disease are common enough to warrant interest yet rare enough to make a statistical study difficult. For this reason a wide diversity of opinion exists with regard to the prognosis. Treatment is notoriously difficult and, all too frequently, unsuccessful. Discussions of this subject are usually fragmentary, consisting chiefly of isolated case reports. In order to clarify the subject we have studied the entire series of pathological fractures observed in the Pondville Hospital (the Massachusetts State Hospital for Malignant Disease) since its opening in 1927.

HISTORICAL REVIEW

Thirty years ago surgeons regarded pathological fractures without hope. Grunert, reviewing the literature from 1886 to 1904, stated, "We are justified in saying that in carcinomatous, that is to say, in true carcinomatous metastases, union of the fragments can never occur. Up to this time there has never been a reported case of such a recovery." He believed that the prognosis was somewhat better in the case of osteogenic sarcoma. "New osteoid tissue may be formed (in sarcoma), yet this seldom leads to a union. At times a true union seems to take place and may exist for a considerable time." However, he cited 4 cases collected by Bruns and added 3 of his own cases that showed an early stage of union at autopsy.

This impression prevailed for a decade thereafter. Cotton, in 1911, said that fractures through carcinoma do not heal. Bloodgood, quoted by Scudder, stated that union rarely followed fractures through metastatic carcinoma. Codman agreed.

Since then many reports have appeared in the literature of healed pathological fractures. Kohler has reported several healed fractures through carcinomatous metastases. Fractures through metastatic hypernephroma have been considered to be exceptionally resistant to healing, yet recently healed cases have been reported by Rypins and Gobbi. Gobbi, in his article, has included abstracts of several other reports of healing of fractures through metastatic carcinoma of other types.

As a result, the prognosis has been viewed more optimistically of late. Pancoast, quoted by Eliason, believes that 40 per cent of cases of pathological fracture due to cancer heal. In the same paper Sampson Handley is quoted as saying that union is the rule. Eliason, however, emphasizes the poor prognosis, which he says is similar to that in sarcoma.

Of 21 cases of bone sarcoma there were 2 cases in which Bloodgood found suggestive ossification. One was his own, the other was recorded by Simmons. Simmons saw partial ossification of the fracture by X-ray and in the amputated specimen. Bloodgood thought much of the bone formation was associated with the neoplasm and not with the fracture.

Coley reviewed 122 cases of osteogenic sarcoma from the Memorial Hospital. There were 26 fractures—an incidence of 21 per cent. In this series union occurred in none. There were 36 cases of endothelial myeloma, of which 26 per cent (9 cases) showed fractures. Union occurred in 3.

The wide disparity of views with respect to healing through metastatic carcinoma is difficult to understand unless such impressions have been based upon an insufficiently large series of cases. That such cases are comparatively rare is attested by MacDonald's figures. He reviewed the fractures of the long bones observed in the Massachusetts General Hospital for a period of 10 years (1910–1920). During this period 1,045 fractures were treated of which 24 were pathological. Three of these cases occurred through metastatic carcinoma, 3 through sarcoma.

THE X-RAY AND THE PATHOLOGICAL FRACTURE

It has long been a disputed question whether or not X-ray treatment is indicated in the treatment of a pathological fracture. Unfortunately it is impossible to obtain any experimental data, derived from animal study, on this problem. In a pathological fracture healing is not as simple as in an ordinary fracture. Tumor cells, when abundant and proliferating rapidly, interfere markedly with the formation of callus. Relatively speaking, the amount of osteoblastic tissue available for repair is greatly reduced. Proponents of the use of X-ray point out that it is necessary to kill those malignant cells in order to allow adequate room for bone repair to proceed. Opponents of the use of X-ray believe that its use will impede the proliferation of connective tissue and osteoid deposition.

There is no reason to suspect that the process of repair of a pathological fracture varies from that following a simple fracture, except in so far as the malignant tissue present tends to slow the repair. For this reason it should be advantageous to review the experimental work done on the relation of X-rays to healing of simple fractures.

Perthes observed in 1903 that if a fowl's wing was treated with X-ray it lagged behind in development. Similar retardation of the growth of young bones was reported in guinea pigs by Trebondeau and Recamier.

Working with fractured radii in rabbits, Salvetti found that after large doses of X-ray (the accurate doses are not given) the bone trabeculæ were smaller than normal, the cartilage cells were frequent, and the calcium salts were deposited more abundantly. He believed this increased deposition of calcium was not a sign of good callus formation, but an attempt of the body to compensate for the thinness of the trabeculæ.

Cluzet irradiated femora of dogs both before and after setting the fractures. He found a diminution of the amount of callus formation. Muller resected sections from the radius in rabbits. He could find no callus stimulation from small doses of X-ray, and believed that they retarded growth.

Fraenkel, in 1914, was the first to ascribe an effect of callus stimulation to the X-ray. He found a considerable shortening of the time of healing in many complicated fractures after irradiation. Kohler, in a clinical study of 87 fractures, found that a light X-ray treatment usually more than halved the time of repair. Krynski, Carrando, Ottolenghi, and Tammann all report beneficial effects from X-ray treatment. Tammann employed 25 per cent of the skin erythema dose on fractures of the tibia in rabbits. The irradiated fractures showed considerable advance in healing in 5 days. After 30 days the repair was still slightly better in the irradiated group. Turco confirmed these findings.

Latten conducted experiments on fractures of the coccyx of rabbits. He irradiated with X-ray varying from 10 to 90 per cent of the skin erythema dose and examined the fractures microscopically each 5 day period for 30 days. He could find no indubitable evidence of callus stimulation from X-ray. But he could find no ill effects arising from light, moderate, or heavy doses of X-ray on healing. He found that healing proceeded so irregularly in different animals that it was hard to evaluate the effect of radiation. He criticizes previous clinical observations, believing that factors such as age, size, and nutritional state are much more important factors than the presence or absence of X-ray measures. Fujanimi has pointed out that fracture healing in various animals proceeds differently. This may explain some of the discrepancies observed by investigators employing different animals. It also throws some doubt on the applicability of any conclusions gained from animals to man.

Fukase experimented with fractured fibulas of rabbits. He fractured both tibias of 84 rabbits, irradiating one side of each animal immediately after the fracture. The other side was used as a control. Because of the splinting furnished by the tibias, the fracture lines were not subjected to unequal forces, such as was the case in many previous experiments. Individual variations in healing were also eliminated in his experiment since both irradiated fracture and control occur in the same animal.

He employed extraordinarily high doses of X-ray in the first experiment. He gave doses of 400r each on four successive days. There were used 170 kilovolts with a 0.5 millimeter zinc filter. Each dose required 15 minutes, and corresponded to 75 per cent of a skin erythema dose. He found that while calcium was deposited in the control fractures in 2 weeks it required 3 weeks after this heavy irradiation. Histologically, for this length of time the irradiated areas were filled with a thick connective tissue, the cells of which resembled bone cells. After 3 weeks numerous vessels appeared and calcium was deposited rapidly.

A series of fractures was then studied using a single dose of 400r. These fractures developed less callus than the normal, while calcification set in earlier and was more rapid than without irradiation. With 200r doses a clear effect on the course of healing could not be recognized.

In summary of the relation of irradiation to fracture healing, it may be concluded that small doses of X-ray produce no significant change, large doses retard healing, and moderate doses, i.e., about 400r, in the hands of most observers, have been shown to accelerate healing.

Therefore, there seems to be no contra-indication to the use of the X-ray in pathological fractures provided that only moderate doses are employed. Not only is healing stimulated, but the amount of malignant tissue interfering with repair is diminished.

Several case reports appear in the literature of pathological fractures treated with the X-ray. Kohler had 2 cases. The first was that of a 51 year old woman who had a carcinoma of the breast. There was an extensive metastasis in the neck of the femur with involvement of the skin and with pathological fracture. Four erythema doses were

given to the femur at intervals of 1 month. The radiation field was 18 by 14 centimeters at a distance of 50 centimeters. One hundred ninety kilovolts with a filter of 0.5 millimeter zinc and 3 millimeters of aluminum were used. There was healing in 5 months. His second patient, 18 years of age, had a metastasis in the humerus, with fracture, from a lymphangio-endothelioma of the sole of the foot. Three erythema treatments were given at intervals of a month. There was healing 3 weeks after the first treatment.

Rypins' case was a man of 46 who had 2 fractures through metastases from a hypernephroma. One fracture through the ulna was given an X-ray treatment of 1000r (200 kilovolts, 4 milliamperes, filtration 2.0 millimeters copper, 1.0 millimeter aluminum, field 10 by 15 centimeters). The other through the tibia received no treatment. Both fractures showed healing 5 months later.

OTHER METHODS OF TREATMENT

Various other methods of treatment of fractures have been suggested. They include the injection of calcium and phosphorus (Albee and Morrison, Haldeman and Moore), excess intake of vitamin A, and the development of acidosis. Mettenleiter has irradiated the thymus of rats and claims more rapid healing of fractures results. We have not been convinced of the value of any of these procedures and have not employed them.

Irradiation of the ovaries, as shown by Dresser and others, frequently leads to bone deposition in metastases from carcinoma of the breast. Sterilization has been employed in nearly all cases of recurrent and inoperable cancer of the breast in this hospital. We have recently begun to sterilize nearly all premenopausal patients with mammary carcinoma.

PONDVILLE CASES

This study comprises all the pathological fractures which have been observed in the Pondville Hospital from its opening in 1927 through December, 1934. It is necessary to define the term "fracture" as employed in this paper. The usual definition of a fracture is a solution of continuity of a bone. In an academic sense, therefore, every metastatic area in bone is a fracture. Cases are not rare in which nearly the entire shaft of a bone, so far as can be determined by X-ray, has been replaced by metastatic disease. Yet the limb clinically shows no localized tenderness and no displacement. These cases have been eliminated; only those cases are included in which a fracture line was distinguished by X-ray, and found to be associated with bone destruction characteristic of a metastatic or primary tumor.

TABLE I.—SOURCE OF PRIMARY TUMOR

	Number	Per cent
Breast	26	49
Lip, mouth, etc.	11	20
Prostate	6	11
Osteogenic sarcoma	5	10
Cervix	2	4
Thyroid	1	2
Liver	1	2
Kidney	1	2
	53	

During this period, there have been 4,739 cases of malignant disease admitted to the hospital. There have been 66 fractures in this group, occurring in 53 patients. Only those fractures in which the evidence clearly pointed to previous malignant disease of the bone are included. This eliminated several fractures through decalcified bone in patients in a poor state of nutrition. Also eliminated are several fractures occurring through areas involved by Paget's disease. Finally those cases in which the fractures were first discovered on the postmortem table are not included since there is no positive proof that the fractures were present before death.

TYPE OF TUMOR

The primary sources of the tumor are listed in Table I. Carcinoma of the breast furnishes the largest number of fractures. During these 7 years 637 cases of cancer of the breast were admitted to this hospital. Of this number 151, or 24 per cent, had osseous metastases. Twenty-six patients, or 17 per cent, showed fractures. Geschickter and Copeland found that fractures occurred in 15 of 100 cases of carcinoma of the breast with bone metastases. Carcinoma of the tongue, lip, floor of mouth, and buccal mucosa frequently involve the mandible by direct extension. Rarely they metastasize to other bones. Cancer of the prostate, of which 161 cases were admitted, showed 78, or 48 per cent, with osseous metastases, but only 8 per cent of fractures. This relatively lower percentage compared with cancer of the breast is due to the hyperplastic character of most prostatic metastases.

Fractures through osteogenic sarcomas are relatively frequent but usually occur late in the disease. It is unusual that we have had only one fracture through a metastatic hypernephroma. There have been 30 cases of renal cell carcinoma observed here, of which 6 had osseous metastases.

BONES INVOLVED

The bones involved are shown in Table II. Of those fractures occurring in the femur, 2 were in

the mid-shaft, 1 in the lower third (through an osteogenic sarcoma). Of the remainder approximately half were in the neck of the femur, the others in the upper third. Only 2 were subtrochanteric. Of those in the humerus, 3 were found in the surgical neck, 1 in the lower shaft, and the remainder in the upper third of the shaft.

Sixteen fractures, or 28 per cent, were found in the flat bones. Considering the large number of metastases that are found in the vertebral column, it is remarkable that fractures are seen so rarely. The vertebræ collapse and mushroom frequently but a true fracture line is extremely rare. Only those cases with a fracture line are included.

PROGNOSIS

It is difficult to evaluate the prognosis after a pathological fracture. Coley believes that the life expectancy of a patient with osteogenic sarcoma through which fracture has occurred is shortened 60 per cent. While theoretically the presence of a fracture should shorten a patient's life, we feel that the majority of such fractures occur in cases of advanced disease, and that it is difficult to prove that a fracture, *per se*, shortens life.

In our series 25 per cent of the patients died less than a month after the fracture. Approximately 25 per cent died in the next 2 months, and another quarter before the expiration of a year after fracture. Eight patients are still living, one 3 years after fracture (#3448—history below), and another 2 years after fracture (#5828—v.i.). Three other patients are living 6 to 8 months after fracture occurred.

The average duration of life after all fractures including cases that are still living is slightly over 6 months. If the carcinomas and sarcomas are separated, the prognosis with respect to length of life is seen to be nearly twice as good in the latter group. In this group the average life was slightly more than a year after fracture, while in carcinomas it was slightly less than 6 months (Table III).

TABLE II.—SITE OF FRACTURE

	Number
Femur	29
Humerus	11
Mandible	10
Pubis	6
Clavicle	4
Rib	2
Vertebra	2
Tibia	1
Ulna	1
	66

TREATMENT

Many of our cases had no specific fracture treatment. This group included, for the most part, those cases in which the fracture was first discovered on routine X-ray examination and in whom there had been no signs or symptoms of fracture. Asymptomatic fractures are relatively common.

In patients with advanced disease, union is so rare that the maximum effort should be directed to making the patient comfortable rather than to securing exact anatomical position. Light traction—about 10 pounds for fractured femora—usually contributes to comfort. More than this weight is usually contra-indicated because of muscular atrophy. Sandbags are occasionally tolerated when traction is unbearable.

Certain cases have a minimum of metastatic disease but receive a fracture. It is in this group that attempts must be made to secure solid union in as short a time as possible. Various types of orthopedic appliances have been employed. We have found a modified Buck's extension to be valuable in the treatment of a fractured femur. Lund swathes are used in fractures of the humerus. We have not attempted surgical manipulation under anesthesia in any case because of the great danger of increasing the deformity. Walking caliper splints are valuable not only for convalescent fractures, but also as preventive devices to be employed in known metastatic disease before fracture occurs.

What is the value of X-ray in the treatment of these fractures? Reference to Table IV indicates that it was employed in only 3 cases of fracture of the femur, 2 cases of fractured humerus, 8 of fractured mandible, and 1 of the pubis. It is necessary to analyze the subsequent progress of these patients in order to see whether or not healing is more satisfactory in this group.

The healing of a fracture may be judged by several criteria. Opportunity has been given to examine many of these fractures after death; absence of the fracture at postmortem is satisfactory evidence of healing. Disappearance of the fracture line by X-ray, provided that there has not

TABLE III.—PROGNOSIS

	Number
Died less than 1 month after fracture	10
Died 1 to 3 months after fracture	11
Died 3 to 12 months after fracture	10
Died 12 to 20 months after fracture	5
Living	8
Data incomplete	9
	53

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1. L. C. Case 5828. February 27, 1933. There is an extensive destructive process involving the right mandible with pathological fracture.

Fig. 2. L. C. Case 5828. This roentgenogram which was taken November 23, 1933, shows that the pathological fracture has united and that there is regeneration of the areas of destruction.

Fig. 3. L. C. Case 5828. March 7, 1935. There is firm union at the site of the pathological fracture and no evidence of disease.

been progressive destruction of the fragments by malignancy, is indicative of healing. On the other hand there are many fractures which, after a period of time, show only partial healing by X-ray. They may have little evidence of new bone or callus formation, but the patients have extremities that can be moved without pain or crepitus. This group we style "fair healing." Some cases have a useless extremity but show slight X-ray or autopsy evidence of healing; this group shows "slight healing." Many cases show no signs of healing.

Of our 65 fractures only 3 (5 per cent) healed. These cases all showed firm union, comparable to that following a simple fracture. Of these, 1 was a fracture of the mandible which received heavy irradiation.

CASE 6828. L. C. This 61 year old man entered the hospital, February 26, 1933, complaining of an ulcer of the cheek of 6 weeks' duration. He had an epidermoid carcinoma, grade I, of the buccal mucosa of the right cheek. There was extensive thickening continuous with the carcinoma extending over the right jaw and into the submaxillary region. The admission diagnosis was carcinoma of the

TABLE IV.—TYPES OF TREATMENT

Type of treatment	Mandible	Femur		Humerus	Pubis	Clavicle	Rib	Vertebra	Tibia	Ulna
		Ca	Sa							
No treatment	2	4	1	2	5	1	2			1
X-ray only	8	1			1					
Traction		9	2							
Cast		3							1	
X-ray and cast		1								
X-ray and traction		1								
Sandbags		1								
Splint		1				2				
Amputation			1							
Swathe				3						
X-ray and swathe				3						
Thomas collar								1		
Not stated		3	1	3		1	1			

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. C. J. Case 204. December 25, 1927. There is mottling and rarefaction in the upper end of the femur. There is an intertrochanteric fracture, with no displacement.

Fig. 5. C. J. Case 204. May 3, 1928. Only the extreme upper end of the fracture line is visible. Areas of rarefaction are much less prominent.

Fig. 6. C. J. Case 204. September 27, 1928. Fracture is well healed. There is extension of metastatic disease in the head and neck.

buccal mucosa with metastases in the neck. X-ray examination by Dr. Dresser was reported to show "an extensive destructive process on the right side of the mandible with pathological fracture. The changes are indicative of malignancy."

He was given 2400r units of X-ray to the right face and neck. (15 by 15 cm. field, 200 k.v., 10 ma., 50 cm. distance, time 14¾ min., w.l. 0.160, filter 4 mm. Cu, 0.5 mm. Al.) He developed a marked X-ray reaction. On May 4 the intra-oral ulceration had disappeared. The X-ray report on this date was "comparison with previous films shows slight enlargement in the defect of the anterior portion of the ramus, but outlines of the bone are definitely smoother."

On May 16 an additional 1200r units of X-ray were given to the right face and neck. On November 23, 1933, a film of the jaw showed "complete union of the bone of the pathological fracture and regeneration of the region of destruction. The lesion of the jaw has now completely healed over. There is union of the fragments of bone and regeneration of the areas of destruction."

On March 7, 1935, there was no evidence of disease.

The second case was a fractured humerus which was found to be healed at autopsy.

CASE 20. H. G. This 55 year old woman entered with carcinoma of the breast. There were fractures of the left femur and right humerus, believed to be of 7 weeks' duration. A swathe was applied to the arm and traction to the leg. X-ray 8 weeks after admission was read as follows: "Film of the right shoulder shows a fair amount of bony callus in the region of the fracture. The entire upper portion of the humerus is involved by tumor. The fracture of the left femoral neck shows very little bony union."

At autopsy, 6 weeks later, "the upper portion of the right humerus was removed and showed a pathological fracture with firm union. The upper portion of the left femur was also removed, which also showed a pathological fracture and rather fibrous union." No X-ray treatment was given to this patient.

The third case was that of a fractured femur.

CASE 204. C. J. This patient, when 45 years of age, had a radical mastectomy for scirrhous carcinoma in July, 1924. She developed a fracture of the right femur in November, 1927. She was kept in traction for 5 weeks and then a plaster spica was applied. In December, 1927, two X-ray treatments were given, centered over the anterior superior spine, and two posteriorly at the same level. (Each was given over a 20 by 20 field, 200 k.v., 5 ma., 25 min., 50 cm. distance, filter 2 mm. Al, 0.5 mm. Cu.)

The cast was removed in February, 1928. Soon after 2 treatments similar to those outlined were given, 1 anteriorly and 1 posteriorly. An X-ray film at this time showed increased calcium deposition. In May, 1928, she was walking with a cane. By X-ray only the extreme upper end of the fracture line was visible. In August, 1928, 4 more X-ray treatments were given, 2 anteriorly and 2 posteriorly to the region of the fracture. A similar course was repeated in October, 1928. Our last X-ray was on September 27, when the fracture line had healed, but there was an increase in the amount of the metastasis. In November, 1928, she was discharged with a walking caliper splint. She died in September, 1929, at home.

In the group that showed fair healing there were 6 cases (9 per cent).

CASE 5392. C. W. This 28 year old woman entered the hospital in November, 1932, complaining of pain in the

Fig. 7.

Fig. 8.

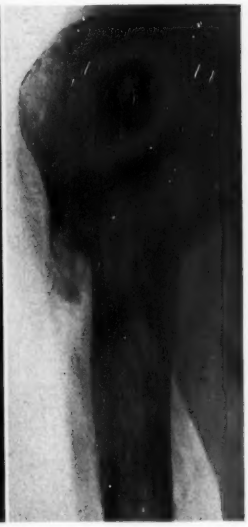

Fig. 9.

Fig. 7. M. M. Case 8705. January 12, 1935. There is diffuse metastatic disease in the upper half of the humerus. A pathological fracture of the surgical neck is present.

Fig. 8. M. M. Case 8705. January 22, 1935. The medial displacement of the lower fragment is more marked. There is no evidence of callus formation.

Fig. 9. M. M. Case 8705. February 18, 1935. There is a moderate amount of callus present. Union is firm clinically.

left hip of 3 months' duration. The X-ray report at this time was: "The intertrochanteric region, head, and neck of the left femur show mottled bone destruction with considerable new bone formation. There is evidence of new bone extending into the soft tissues. There is apparently a spontaneous fracture through the neck of the femur." 800r units of X-ray were given both anteriorly and posteriorly over the fracture. (15 by 15 field, 10 ma., 200 k.v., 4 mm Al, 0.5 mm. Cu. filter, 200r per treatment.)

In January, 1933, the fracture line was no longer visible. At this time the left hip was ankylosed at 45 degrees. During the next 6 months the patient's liver gradually enlarged and she developed ascites. Three months before death 600r of X-ray were given over the left hip, anteriorly. Death occurred in July, 1933. At autopsy a bile duct carcinoma metastatic to the left femur was found. The autopsy report read: "The region of the trochanter, neck, and head of the left femur are occupied by a tumor mass, involving the soft tissues and the ilium. It is firm in consistency and on section is yellowish-white in color. It contains a large amount of new-bone formation."

Case 3448. S. Y. In November, 1930, this 30 year old woman sustained a fracture of the lower end of the femur. through what was believed to be a bone cyst. A plaster cast was applied. She was first admitted to this hospital in June, 1931. At this time the patient was walking with a slight limp, because of slight pain on weight bearing. X-ray showed "an extensive pathological process involving the supracondylar area of the left femur. The cortex is broken on both sides of the bone. Apparently there is a spontaneous fracture." Amputation was done in August. The specimen was described as follows: "The medullary cavity at the epiphysis of the femur is filled with a friable, gray-green material, and the edges of the cavity are replaced by tumor tissue. The periosteum is intact except in one portion where there is a recent, irregular fracture with a moderate amount of callus and bone formation. Microscopically pleomorphic spindle shaped cells closely packed are found. Atypical and typical mitoses are very numerous. There is a moderate amount of hemorrhage and necrosis. Diagnosis: osteogenic sarcoma (fibrosarcoma)." The patient was alive and well November 21, 1934, without evidence of recurrence.

This patient had no X-ray treatment.

Case 248. L. W. This 44 year old woman entered the hospital 18 months after a mastectomy for carcinoma. X-ray showed multiple bone metastases. She received 2 X-ray treatments, 1 over the left sciatic notch, and 1 over the left lower femur; these treatments were given 2 weeks after she complained of severe pain in her left hip. (Treatments were given over a 20 by 20 field, 50 cm. distance, 200 k.v., 5 ma., filter 0.5 mm. Cu, 2.0 mm. Al.)

Two months later by X-ray "the upper end of the femur at the level of the lesser trochanter showed definite outward bowing with evidence of a fracture that has apparently been healed. No trace of this was visible at the previous examination." The patient was kept in bed 2 months. She then rested weight on her left femur, and it snapped at the site of the old pathological fracture. The leg was then put up in traction. Four months later X-ray showed lateral displacement of the upper fragment. She died 11 months after entry.

Case 8352. G. K. In 1932 this 49 year old woman had X-ray treatment for a carcinoma of the breast. She en-

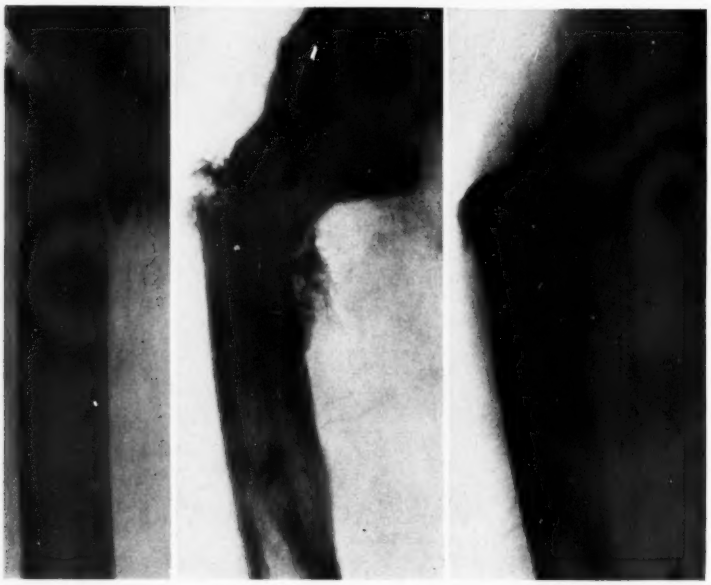

Fig. 10. Fig. 11. Fig. 12.

Fig. 10. J. F. Case 8088. October 30, 1934. There is extensive bone proliferation in the upper part of the left femur and pelvis, combined with some areas of destruction. There is a transverse fracture of the shaft just below the trochanters.

Fig. 11. J. F. Case 8088. January 14, 1935. There is a moderate amount of new bone formation. Fracture line is clearly visible.

Fig. 12. J. F. Case 8088. February 18, 1935. There is now considerable new bone formation. The fracture line is indistinct but still present.

tered this hospital August 31, 1934, with a pathological fracture of the upper end of the shaft of the right humerus. 1200r units of X-ray each were given centered over the anterior and posterior surfaces of the right shoulder joint. (20 by 20 cm. field, 200 k.v., 10 ma., 50 cm. distance, 4 mm. Al, 0.5 mm. Cu filter, 400r each treatment.)

X-ray on November 8 showed new bone forming by the fracture. In February, 1935, the right arm was practically useless although there was apparently firm union in a bad position. X-ray examination, however, revealed no change since the previous examination.

CASE 8705. M. M. This patient entered this hospital in November, 1934, when she was 63 years of age. She had had a simple mastectomy for carcinoma in 1930. Recurrences had been removed twice thereafter. A breast series was negative at entry. The patient had numerous recurrences along the scar. A radical mastectomy was done. Two months afterward the patient began to complain of pain in the right shoulder and shortly afterward received a fracture of the surgical neck of the humerus. The patient had received 300r units of X-ray daily, directed over the posterior surface of the right shoulder joint, on the 2 days preceding and including the fracture. (15 by 15 cm. field, 20 ma., 200 k.v., 50 cm. 0.160 w.l., 4 mm. Al, 0.5 mm. Cu filter.)

After 3 weeks' treatment by means of a Lund swathe alone, there was no evidence of new bone formation. 600r units of X-ray were then given to each of the anterior and posterior surfaces of the right shoulder. The patient was discharged about 7 weeks after fracture. By X-ray there was evidence of a small amount of new bone formation. The arm could be moved without pain and there was no tenderness. Patient reported to the clinic in September, 1935. At this time bony union was present, although there was still marked irregular thinning of the upper end of the humerus.

CASE 448. G. W. In July, 1926, this 36 year old woman received X-ray therapy elsewhere for a carcinoma of the breast. In March, 1928, she sustained a pathological fracture of the left femur. She was placed in a plaster spica. She first entered this hospital in April, 1928. On June 25 there was a fracture of the surgical neck of the right humerus, through an area of metastatic disease. On August 9 an X-ray film of the hip showed no visible callus formation. At this time the patient had good use of her right arm and, clinically, firm union at the site of the fracture. No X-rays of the humerus were taken, however, after the initial plate. The patient died in December, 1928. No autopsy.

In the group that showed slight healing there were 4 cases (6 per cent).

CASE 20. H. G. History has been given.

CASE 8316. M. S. This 67 year old woman entered the hospital nearly moribund, with carcinoma of the breast metastatic to skull, vertebræ, pelvis, and lung. X-ray showed an old pathological fracture of the left femur, with evidence of slight healing. No treatment was given. She died 6 days after entry. There was no autopsy.

CASE 8088. J. F. This man of 75 years was admitted to the hospital with a pathological fracture of the left femur, subtrochanteric, in October, 1934. His prostate was moderately large and firm with thickening about the left upper pole. Hyperplastic metastases were visible in the left femur and ilium. Buck's extension with 10 pounds traction was applied. Two months after fracture, the patient could stand for a few moments on his leg. At this time there was a large amount of new bone formation, but the fracture line was still visible. In February, 1935, the fracture line showed no healing, but the fracture was firmly united to palpation. At this time the patient was discharged against advice, having been confined to his bed for the past month.

CASE 3442. A. P. This 61 year old man entered in January, 1931, with acute retention. He received radium implantation and suprapubic cystotomy for carcinoma of the prostate. He received X-ray therapy to the pelvis. He sustained a fracture of the upper end of the shaft of the left femur in June, 1932. He was placed on Buck's extension. An X-ray in October, 1932, showed angulation and overriding of the fragments but considerable new bone formation. At this time the union was firm clinically. However, the patient never got out of bed after the fracture. He died in February, 1933. At autopsy the fracture was still present.

SUMMARY

In 53 cases (80 per cent) we obtained no evidence of healing.

The methods of treatment may be summarized as follows: In the cases with satisfactory healing one had heavy X-ray alone. One case had fixation and X-ray in moderate dosage. One had fixation alone. In the 6 cases with fair healing 2 cases, 1 of which was an osteogenic sarcoma, had fixation only. Three had a moderate amount of X-ray; in 2 of these cases it was combined with fixation. One had a small amount of X-ray with no other treatment. Of the 4 cases that showed slight healing 3 had traction only; 1 case had no treatment in this hospital. None had X-ray for treatment of the fracture.

Of the 52 cases that did not heal, 8 received X-ray treatment with no benefit. These cases included 1 fracture of the pubis, 7 of the mandible. It should be noted that fractures of the mandible form what should be considered a distinct group. They are compound fractures, all grossly septic. Moreover, there is frequently wide separation of the bony fragments. They are therefore the most resistant of all fractures to treatment.

A question of great importance is whether or not X-ray treatment of a bone metastasis is of any value as a prophylactic against fracture. We have treated only an occasional case before fracture, so at present are unable to advance any data on the problem.

Other factors than X-ray treatment are of course of great importance in the prognosis of fractures. The condition of the patient must be considered. The best results may be expected in patients who are in good general health and who have a single bony metastasis.

CONCLUSIONS

1. Sixty-six pathological fractures occurring through carcinoma or primary osteogenic sarcoma are reported.

2. Experimental study reviewed shows that treatment of a simple fracture with moderate doses of X-ray accelerates healing.

3. Five per cent of our fractures healed with firm union. Nine per cent showed moderate healing. Six per cent healed slightly. No evidence of healing was obtained in 80 per cent.

4. Of our 9 fractures that healed, either fully or moderately, 6 cases received X-ray therapy to the bone after the fracture.

5. In our series the average length of life following fracture through carcinoma was slightly less than 6 months. After fracture through osteogenic sarcoma, the length of life averaged slightly over a year.

NOTE.—The author thanks Dr. E. M. Daland, surgeon-in-chief, Pondville Hospital, for suggestions in preparation of this report, and Dr. Richard Dresser for use of his X-ray plates.

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LYMPHOPATHIA VENEREUM—"LYMPHOGRANULOMA INGUINALE"—OF THE FEMALE URETHRA

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CHRONIC inguinal adenitis, frequently progressing to suppuration with multiple draining sinuses, occurring chiefly in men and only occasionally in women, has been described for over half a century and under many names. Durand, Nicolas, and Favre described the condition in 1913, realizing that it was not a new disease and that it had been portrayed by many previous authors. Their work served to draw attention to this clinical entity. They proposed the name "lymphogranuloma inguinale," thinking the microscopical picture was similar to Hodgkin's disease. Unfortunately, this confusing term has since then been widely used, although it has been clearly demonstrated that there is no relation or real similarity to Hodgkin's disease. While the disease was studied by many investigators, no great progress was made until Frei (9), in 1925, discovered a specific diagnostic antigen prepared from the bacteriologically sterile pus[1] from these cases. His intradermal test gave impetus to worldwide studies. The disease has been transferred to monkeys and mice (Hellerström and Wassén, Levaditi, Ravaut and Lépine, Findley, and others), producing a characteristic meningitis after intracerebral inoculation; to guinea pigs (Meyer, Rosenfeld, and Anders), producing a typical inguinal adenitis after inoculation in the groin; and to other animals. The filterable virus nature of the causative agent has been made clear by a number of investigators (Hellerström and others). Recently, Tamura claimed to have cultured the virus, using special media, and to have reproduced the disease in guinea pigs from the cultures. "Lymphogranuloma inguinale" is now generally accepted as a proved disease entity.

By means of the Frei test several other interesting clinical conditions have been linked with "Lymphogranuloma inguinale." The association of large labia with ulceration of the skin and vaginal mucous membrane, hypertrophic tags about the rectum, and sometimes with rectal stricture, has been recognized for very many years. The terms elephantiasis vulvæ, esthiomène, chronic hypertrophic vulvitis, and genito-ano-rectal syndrome have been used to indicate this disease. It was perhaps due to Fournier who in 1875 gave the name "anorectal syphiloma" to the hyperplastic infiltration which leads to stricture of the rectum, that syphilis has been most widely considered the cause of this syndrome. Not only syphilis, but tuberculosis, chancroid (Ducrey infection), gonorrhea, and, in more recent years, granuloma inguinale have been ascribed as causes in a most extensive literature. The development of knowledge concerning granuloma inguinale made it clear that syphilis and other conditions mentioned were rarely, if ever, the cause of esthiomène. For a period of years it was thought that all cases were due to granuloma inguinale. Some contemporary authors have considered that esthiomène is due to a combination of diseases and local injuries (Stein, Taussig).

Since 1928 when Frei and Koppel (11) first reported positive Frei tests in a small series of patients with esthiomène and rectal stricture, numerous other publications have appeared in support of the "lymphogranuloma inguinale" virus as the cause of these conditions (Bartels and Biberstein, De Wolfe, Lee and Staley, and others). Bartels and Biberstein have given their interpretation of the pathogenesis, showing that the infection has an especial tendency to involve the lymphatics.

They believe that the predominance of rectal stricture in women is due to the fact that the lymphatics of the posterior wall of the vagina and the fourchette drain to the subperitoneal surface of the rectum where they join with the lymphatics coming from the rectal submucosa. Such an explanation, however, involves the assumption of a retrograde transport of the virus through the wall of the rectum into the submucosa, where the oldest and most prominent lesion of rectal stricture is found. It is possible that this could be effected by progressive septic thrombosis of the lymphatics. The more common location of the lesion in the ampulla is attributed to the unusually rich mucosal lymphatics in this region.

A proper understanding of the clinical forms of this virus disease has been difficult because of the unfortunate name "lymphogranuloma inguinale." The disease is confused with Hodgkin's disease, commonly called "lymphogranuloma," but which has no known relation to the condition under

[1]The use of pus as an antigen has certain disadvantages. Grace and Suskind (Proc. Soc. Exper. Biol. & Med., 1934, 32: 71) have advised the use of a mouse-brain antigen. It is likely that such a preparation from infected animal material will prove more satisfactory than the original Frei antigen.

consideration. It is also confused with granuloma inguinale, a quite different disease, primarily affecting the skin and caused by Donovan's organism. "Lymphogranuloma inguinale," as shown by the Frei test, is by no means limited to the inguinal region. However, several authors have demonstrated that the inflammatory reaction characteristically extends along and blocks the lymphatics. Its venereal nature has been alluded to by many. Wolfe and Sulzberger propose the name "lymphopathia venereum" an apt, clear, distinguishing, and descriptive term, and one that will hereafter be used in this paper.

The purpose of this paper is to present a series of 11 cases which seem to indicate the stages of a syndrome occurring in women, beginning with a chronic urethritis and progressing to urethral stricture or extensive urethral ulceration. Nine of the 11 are associated with positive Frei tests.

Chronic abacterial urethritis, in which no bacteria could be cultured or could be ascribed as a cause, was perhaps first described by Waelsch in 1904. So far as we know, his work and this condition have received no recognition in this country.

Curth in 1931 described a male patient with enlarged inguinal lymph nodes and urethritis. A smear of the discharge from the urethra showed leucocytes but no bacteria. The patient himself showed a positive Frei reaction, and an antigen prepared from the urethral discharge acted as a specific Frei antigen. In 1932, Frei (10) reported a case of chronic abacterial urethritis in a young man with negative Frei test. However, an antigen prepared from the urethral discharge did act as a specific antigen when injected into patients with known lymphopathia venereum. But the discharge when injected into a monkey did not produce the typical encephalitis. Kalz (14), in 1933, presented 3 patients with the Waelsch type of urethritis with negative Frei tests. From the urethral discharge of each an antigen was prepared, which acted similarly to known Frei antigen. There has been some discussion of the cases of Frei and Kalz, as to whether the original patients had anergy, whether the lesion was too superficial to produce allergy, or, whether the urethritis in these cases was due to a virus which was different from, but closely akin to, that of lymphopathia venereum. Polak (1933) described 3 carefully selected cases in which an abacterial urethritis was associated with large inguinal lymph nodes and positive Frei reaction. Bezecny (1934) presented another case of chronic non-gonorrheal urethritis with strongly positive Frei test, and the specific antigen was recovered from the urethral discharge. All of these patients were men.

Various ulcerations of the vagina have been reported as associated with esthiomène or rectal stricture and with positive Frei reaction. These ulcerations have been found more commonly about the fourchette. Richter (1932) described an extensive ulceration of the entire anterior vaginal wall with a smaller ulceration in the fourchette, occurring in a woman of 25 years. The urethra was not mentioned as being involved. The Frei test was positive. The patient also had syphilis, but intensive anti-syphilitic treatment had no effect on the lesions.

Weissenbach, Martineau, and Fourestier (1934) reported the case of a 44 year old woman with rectal stricture, urethral infiltration, and incontinence of urine. The interior of the urethra was edematous, congested, and there was a false purulent membrane. The Frei test was positive. Serological tests for syphilis were negative. This is the only report in the literature of involvement of the female urethra of which we are aware.

CASE REPORTS

CASE 1. E. J. The patient, a negro female of 41 years, was first seen in 1934 complaining of severe burning and straining on urination with nocturia (12 times a night) for 3 months. Five years previously her physician told her she had inflammation of the womb and bladder. For 3 years she had had urgency of urination and had been occasionally incontinent. The uterus was three times normal size. There was slight pyuria. Bladder cultures showed on one occasion a few colonies of Bacillus coli, on another Staphylococcus albus. A hysteromyomectomy was done, but with no relief of the bladder symptoms. In 1935 the external genitalia were normal, the cervix normal and well suspended, and no rectal lesion was found. The inner part of the urethral meatus was slightly injected. No purulent material could be expressed. Urethroscopic examination showed marked injection along the course of the urethra, but no ulceration. The bladder appeared normal. Repeated cultures showed no growth. Repeated Wassermann tests gave negative reactions. Local applications of silver nitrate gave no benefit. Frei reaction was positive. After more than 1 year of treatment, the patient remained no better.

CASE 2. D. S. The patient, a negro female of 29 years, was first seen in 1934, complaining of diurnal urinary frequency every 15 minutes, and nocturia 5 to 6 times, beginning 2 days previously. There was occasional incontinence, some dribbling, and slight dysuria. Three years previously, because of a positive Wassermann reaction, she was given 10 doses of diarsenal and 10 of bismuth in another clinic. Examination showed no palpable inguinal glands, normal external genitalia, and negative pelvic and rectal findings. A small point-like projection was found on the posterior margin of the urethral meatus, which looked like a valve and had the appearance of normal vaginal tissue. There was a definite obstruction at the junction of the internal urethra and bladder. On the right side of the internal urethra near the junction with the bladder, a definite ulcer, triangular in shape, was found, which bled freely. The bladder and trigone appeared normal. Numerous cultures showed only varying organisms which are commonly considered contaminants. The stricture was gradually dilated,

and silver nitrate 3 per cent and gomenol were applied to the urethra. In 1935 after many treatments the symptoms showed little or no improvement. The urethra was diffusely injected and granular. Repeated Wassermann reactions were negative. Frei reaction was positive. During a year of treatment the symptoms were improved at one time but soon returned and showed no improvement.

CASE 3. C. H. The patient, a negro female of 43 years, was first seen in 1931 complaining of dysuria and straining on urination. It began 3 years before, with marked frequency and nocturia 10 times. Twelve years previously she had had a sore on one labium and 7 years before she had 12 intravenous injections at another hospital. On examination the external genitalia were normal. The posterior wall of the anterior two-thirds of the urethra was missing, but there was apparently no fresh ulceration. In addition there was a marked stricture in the region of the internal sphincter. There were myomata uteri. Rectal examination was negative. Cultures from the bladder yielded organisms that were regarded as contaminants (diphtheroids). After dilatations of the urethra, a hysteromyomectomy was done. One of several Wassermann reactions was positive, and she was given 16 doses of diarsenal and 15 of bismuth. In 1935 she returned complaining of marked pain in the bladder and renal regions, with much dysuria and straining on urination. The external genitalia were normal. Two thickened folds were found on each side of the urethral meatus which was situated about 1.5 centimeters back of its normal position, and involved in a healed ulceration. With great difficulty the urethra was again dilated. The remainder of the pelvic and rectal examinations were negative. Wassermann reactions were negative; Frei reaction positive. The urinary symptoms and the urethral stricture have been temporarily helped by treatment.

CASE 4. A. P. The patient, a negro female of 53 years, was first seen in 1920 at the age of 38, complaining, for 20 years, of dysuria and of passing her urine in small amounts frequently and slowly. One year previously she had a sore on one labium, which lasted only a few days. For 2 weeks she had had constant dribbling. Examination showed normal external genitalia. There was a fold of vaginal mucosa, which had evidently been distorted by an inflammatory process, stretched across the urethral orifice in a bridge-like formation. After the band was cut the meatus was found extremely small. A small probe indicated the lumen. With some difficulty the urethra was dilated. In 1935 she returned complaining of severe pain and great difficulty in emptying her bladder. There has been marked frequency, nocturia, and slight incontinence. Examination showed normal external genitalia. The anterior part of the urethra was missing, being replaced by healed scar tissue. The orifice was found with difficulty, being extremely small and situated about 2 centimeters back of its normal position. With more difficulty it was dilated. The remainder of the pelvic and rectal examinations were negative. Repeated Wassermann reactions were negative; Frei test negative. The ulcerative process was long ago completely arrested.

CASE 5. M. S. The patient, a negro female of 32 years, was seen in 1929 complaining of vaginal bleeding following intercourse, and nocturia. A year previously, both she and her husband had had inguinal buboes which were incised and drained several weeks. On examination there was found an inguinal scar, but the glands were not enlarged. A small caruncle of the external urethral meatus was found. The pelvic organs and rectum were normal. The uterus was curetted, normal endometrium obtained, and the caruncle was fulgurated with high frequency current. Following this, redness and induration persisted about the urethra, and there was some dysuria and nocturia. In 1930, she contracted gonorrhea, proved by urethral smear. In 1933, she returned with backache, dysuria, frequency, partial urinary incontinence, and some hematuria. A reddened caruncle surrounded the meatus and three small punched out ulcerations were found on the lower part of the right labia. Dark field examinations for spirochetes were negative on several occasions. A diffuse stricture of the urethra and marked injection of the outer half of the urethra were present. Eight cultures from the urethra on separate occasions were either sterile or gave varying organisms considered contaminants. In 1934, the urethra was eroded to the internal sphincter which was the site of a stricture. In 1935 she had practically no urinary complaints, was voiding easily, and while the urethra was found largely eroded away the ulceration appeared healed and not injected. Biopsy of the ulceration showed chronic inflammatory tissue. Several Wassermann reactions taken over several years were negative. As for treatment, the urethral caruncle was originally fulgurated, which apparently helped none. Silver nitrate was occasionally applied to the ulceration, and the stricture was dilated as it became necessary. A recent Frei test was negative. The ulceration was almost completely healed.

CASE 6. S. J. The patient, a negro female of 38 years, was first seen in 1932 complaining of headaches and pains in the lower abdomen. At 19, she had had gonorrhea, followed a few years later by a genital sore causing a swelling on one side of the vulva, which afterward disappeared. In 1926 she took needles for "bad blood" for 9 weeks, at another hospital. It was not definitely known that this patient had had syphilis. Examination showed normal external genitalia, and there was no urethral lesion. A diagnosis of chronic salpingitis and retroposition of the uterus was made. Although the Wassermann reaction was negative, and continued so on 21 occasions, she was at that time given 8 doses of bismuth and 6 doses of neo-arsphenamine. In 1933, she returned with more marked urinary symptoms and a diminution in the size of the urinary stream. A small shallow ulcer with clean, freely bleeding base and measuring 2 centimeters across was found destroying the urethral meatus. She was given 6 doses of neo-arsphenamine and 5 doses of bismogenal, while there was slow progression of the ulceration. In 1935, the patient had a deep ulceration with a pinkish gray, firm, polypoid base which had destroyed about 2 centimeters of the urethra. A biopsy of the ulcer showed chronic inflammatory tissue. Frei reaction was strongly positive. The ulceration was slowly progressing.

CASE 7. R. D. The patient, a white widow of 35, was seen in 1935 complaining of ulceration about the urethra for 1 year, which began as an "abscess" in the urethra. After a short time the abscess ruptured and did not heal. For 4 to 5 years she had had burning and stinging on urination, with some dysuria. These symptoms have been much more aggravated since the ulceration developed. Several previous Wassermann reactions were negative, and a biopsy had shown chronic granulation tissue. Three X-ray treatments had been given with no improvement. On examination the external genitalia were found normal. The anterior urethra was completely destroyed by a deep, reddened, undermining ulceration, with undulating thickened borders of the vaginal mucous membrane. The base of the ulceration was quite red and polypoid, into which at some point the urethra opened. The remainder of the pelvic and rectal examination was negative. Repeated Wassermann tests gave negative reactions. Biopsy again showed chronic granulation tissue. Cultures for fungi were negative. Frei reaction was positive. The ulceration appeared to be slowly progressing.

CASE 8. C. J. The patient, a negro female of 20 years,

Fig. 1. Case 8. Undermining ulceration has destroyed the anterior part of the urethra. The orifice opens below the symphysis, which is clearly seen. A small fistula is present immediately below the clitoris.

was seen in 1933, complaining of pain in the right shoulder and leg, burning on urination and nocturia. The external genitalia and urethral meatus were normal. Cervical smear was positive for Gram negative intracellular diplococci. Wassermann reaction was positive. X-ray showed a periostitis of the left tibia, attributed to syphilis. Eight injections of neo-arsphenamine were given with marked improvement in the bone lesion. Treatment was continued in another clinic with 8 doses of diarsenal and 6 of bismuth. After 7 months of treatment and with no apparent difficulty from the gonorrheal infection, a small punched-out ulcer appeared below the clitoris, with surrounding hyperemia and tenderness. Gentian violet and mercurochrome were applied locally. Forty-eight cubic centimeters of a 1 per cent solution of tartar emetic were given intravenously in divided doses, and she was given 12 injections of neo-arsphenamine and 4 of bismogenal, while the ulceration proceeded to destroy the anterior two-thirds of the urethra. The base of the undermined ulcer was very red and extremely tender. In 1935 the inguinal glands were just palpable, the largest about 1 centimeter across, and the labia, prepuce, and clitoris appeared normal. The anterior urethra was completely destroyed by an undermined ulceration with thickened undulating borders, the base of which was made of grayish-red, firm, polypoid tissue. The curving arch of the symphysis was readily seen. The pelvic organs and rectum were normal to palpation. Frei reaction was positive. The progression of the ulceration showed no evidence of being arrested.

Case 9. F. A. The patient, a negro female of 53 years, was first seen in 1930. Her menopause was in 1928, following which she developed marked soreness in the region of the vagina. Since then she had had a yellowish discharge, occasional spotting of blood, frequency and burning on urination, with occasional incontinence. There was nocturia one to three times. On examination, inguinal glands were not palpable, and external genitalia were normal. The anterior vaginal wall was greatly thickened, corrugated, indurated, and dry. The urethral meatus was normal. Two false orifices near the meatus did not communicate with the urethra. The remainder of the vagina, cervix, and rectum were normal. There were myomata uteri. Wassermann reaction was positive, and she was given 3 doses of neo-arsphenamine and 3 of bismuth. In 1932 there was a severe constant burning sensation in the region of the urethra and frequent bleeding from the vagina. A soft granulomatous lesion several centimeters across was found involving the urethral meatus. Six doses of bismuth, 90 cubic centimeters of tartar emetic (1 per cent) in divided doses, 2 doses of arsphenamine, and 13 doses of silver arsphenamine were given in succession. In 1933 the symptoms were not improved, and there was nocturia 4 to 5 times. Examination showed the urethra opening into a large excavation with finger-like processes, easily admitting the finger tip, bleeding easily, and quite painful. A part of the overhanging mucosa was removed, and the bed of the ulcer fulgurated with unipolar current. Five doses of bismuth and 140 cubic centimeters of tartar emetic in divided doses were given. In 1935 the urinary symptoms had shown no improvement. The inguinal glands were not palpable. The labia majora and clitoris were slightly edematous. The deep, dirty red, granular ulceration extended under the clitoris and beneath the skin of the right labium majus forming a small perforation. The urethra opened into the ulceration far up beneath the symphysis. The cervix and rectum were negative. The myomata uteri had not increased in size. Several biopsies showed only chronic granulation tissue. Frei test was strongly positive. The ulceration showed no healing.

Case 10. C. A. The patient, a negro female of 25 years, was seen in 1934 complaining of marked urgency on urination, dysuria, nocturia, chills, fever, and pain in the right flank. Acute cystitis and pyelitis were evident. Examination showed the clitoris, right labia, majus and minus, swollen, dotted with small raw areas. The anterior urethra was destroyed by an old ulceration extending behind the symphysis pubis and down the left side of the vaginal orifice. The cervix and uterus were normal. Both adnexa were enlarged, fixed, and tender. Urine cultures showed Bacillus aerobacter aerogenes and Bacillus coli. The acute symptoms soon subsided. In 1935, she had slight burning on urination and slight incontinence, but no pain, dysuria, or hematuria. A chain of inguinal glands was just palpable in each inguinal region. The right labium majus was three times normal size, the left slightly swollen. The clitoris was large, measuring 3 by 5 centimeters. The urethral meatus was completely destroyed by a deep ulceration with firm, red, polypoid base. The arch of the symphysis pubis was clearly seen, and the cavity admitted one finger up to the internal sphincter of the bladder. Rectal examination was normal. Biopsy from the ulceration showed chronic granulation tissue. Culture from the bladder yielded only Bacillus lactis aerogenes. Repeated Wassermann reactions have been negative. Frei test was positive. There was no evidence that the ulceration was healing.

Case 11. L. J. The patient, a negro female of 22 years, was first seen in 1927 with a macular rash over the body and a positive Wassermann reaction. The labia were slightly swollen, and there were small ulcerations on the clitoris and both labia majora. She was given 9 injections of neo-arsphenamine and 5 of bismuth, and the ulcerations healed. In 1929, a small, very hard, granular, oval ulceration was found on the inner surface of the left labium majus. Several inguinal glands, 1 to 2 centimeters in diameter, were palpable on each side. Dark field examination and Wasser-

mann reaction were negative. In 1930, the labia appeared normal. In 1931, a small lesion on the vulva was dark field positive for Treponema pallidum. The vulva was swollen and edematous. Wassermann reaction became positive, and the labia became more edematous. A large ulcer appeared on the left labium majus with ragged edges and dirty gray base. Five doses of arsphenamine and 55 cubic centimeters of tartar emetic were given in divided doses as the lesions progressed. Malaria inoculata was given, resulting in 12 chills. The labia were enormously swollen with hard, raw, indurated areas between the labia, and a boil-like localized lesion appeared on the left buttock. Ten doses of neoarsphenamine and 155 cubic centimeters of tartar emetic in divided doses were given, with practically no change. In 1935, the patient complained of frequency and burning on urination and nocturia, 2 times. There was a constant dull aching pain in the vaginal region. On examination the inguinal glands were found palpable but not definitely enlarged. Both labia majora were very large with induration in the skin. A deep ulceration had destroyed the urethral meatus, extended around the introitus and formed deep pockets on each side of the rectum, more on the right side. The vagina behind the ulceration and the cervix appeared normal. Rectal examination was negative. Frei test was positive. There was no evidence that the ulceration was healing.

From the histories and physical findings of these individual cases, certain characteristics of the urethral lesions group themselves to form a syndrome. The disease apparently begins as a chronic urethritis, which may be accompanied by an intra-urethral ulcer, and may remain stationary for years, with or without treatment. Apparently, if the inflammatory reaction extends deeply into the tissues, the disease may proceed so slowly as to allow progressive formation of scar tissue, resulting in stricture of the lumen. The stricture may occur at any point, but is most commonly near the internal sphincter. In some cases the inflammation extends at a steady rate, involving most severely the urethral meatus, resulting in ulceration of the orifice. The ulceration may proceed, causing all degrees of destruction of the urethra and surrounding vaginal mucous membrane, although we have not seen complete destruction of the internal urethral sphincter or base of the bladder. These ulcerations have a firm, granular, polypoid base, 0.5 to 2 centimeters deep, with characteristic thickened, undulating, undermined borders. The base may be very red, extremely tender, and may bleed easily, or it may be gray, granular, and insensitive. The ulceration may be entirely replaced by the contraction of scar tissue, and a lesion may be partially or entirely halted in such a manner at any point. The ulceration may extend around the introitus and burrow deeply to each side of the rectum. There may or may not be an associated elephantiasis of the vulva.

Six of the 11 cases presented in this paper have had syphilis and have been treated with arsenic and bismuth preparations. These cases follow.

Fig. 2. Case 10. Elephantiasis of the labia majora and clitoris accompany a deep ulceration destroying the urethra up to the sphincter.

One of the 2 patients with chronic urethritis had syphilis. Her urinary symptoms began shortly after a rather thorough course of antisyphilitic treatment.

One of the 2 patients with urethral stricture had syphilis. Symptoms from the stricture began several years after antisyphilitic treatment, and the stricture was not helped by repeated antisyphilitic therapy.

Four of the 7 patients with definite ulceration about the urethra had syphilis, and in each of these cases the ulceration appeared during the time the patients were under observation and receiving antisyphilitic treatment. Furthermore, a continuation of vigorous antisyphilitic treatment not only had no effect on healing the lesion but was accompanied by a progression of the ulceration in each case. The 3 other cases with ulceration, having almost precisely the same characteristics, had repeatedly negative serological tests for syphilis. In fact, one of the latter with a typical ulceration of 2 years' duration showed in 1935, the greatest degree of healing of any of the patients with ulceration, and had received only hygienic local treatment in addition to local applications of silver nitrate.

Biopsies were taken from 5 of the 7 patients with ulceration. In each case sections showed for the most part a chronic granulation tissue with rather marked proliferation of the endothelium of the capillaries and a marked infiltration with plasma cells and lymphocytes. In addition there

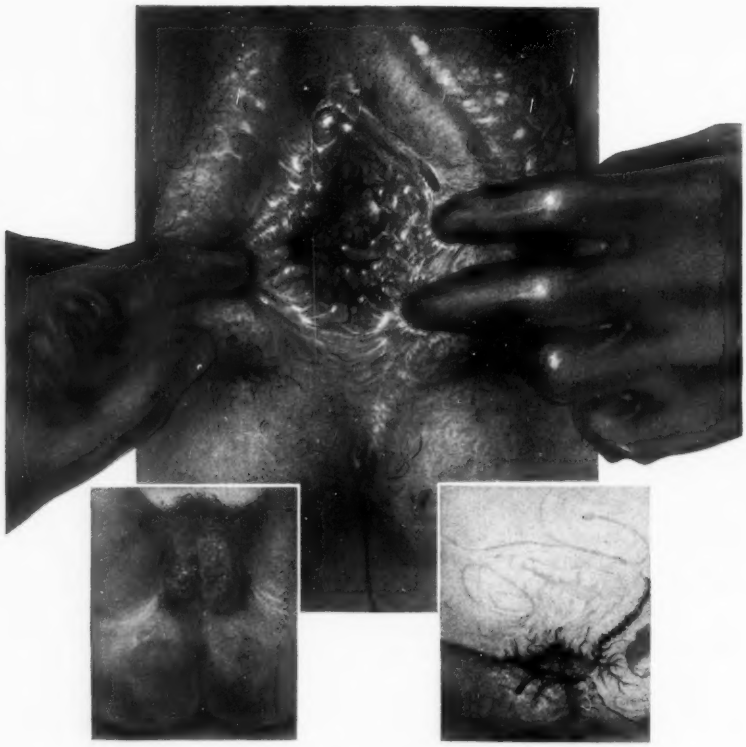

Fig. 3. Case 11. External genitalia of a 22 year old negress showing elephantiasis vulvæ and complete ulceration of the vestibule. The urethra opens in the depth of the ulceration and hypertrophic tags surround the vaginal orifice. To the right of the vaginal orifice the ulceration extends more deeply in the region of Bartholin's gland. The skin over the buttocks shows induration with superficial infection (left insert). Sagittal section shows extent of the ulceration, which destroys the anterior urethra and vagina (right insert). A probe designates the depth of the ulceration in the region of Bartholin's gland.

were scattered polymorphonuclear leucocytes, and occasional eosinophils and mast cells. The surface epithelium where present showed some hyperkeratosis with scattered polymorphonuclear and round cells through the squamous cell layer. The rete pegs at the edges of the ulcer were greatly prolonged, and the basal cell layer, in some areas, became two and three layers thick. However, the basal layer was intact and no mitotic figures were seen. In some cases there was great scarring in the submucosa. No obliterative changes were seen in the small vessels.

Histologically, no formation of tubercles was found. Kinyoun stains of the cases with biopsies were negative for tubercle bacilli. Other bacterial stains revealed no bacteria within the tissue itself, although Gram positive and Gram negative cocci and bacilli were present in relatively small numbers in the surface débris. No organisms with the morphology of Ducrey's streptobacillus were found. No Gram negative diplococci, either intracellular or extracellular, could be demonstrated. Wright's stains showed no Donovan bodies.

Frei tests were performed on the 11 patients, with positive results in 9. One patient (Case 4) with a negative test was a negro woman with scarred retracted urethral meatus and urethral stricture, first discovered in 1920, and at that time the history of the lesion dated back 20 years. No active ulceration has been observed. The other patient (Case 5) with a negative test was a negro woman with an ulceration quite similar to the

others in this group, which destroyed the anterior portion of the urethra, but which was gray, scarred, and insensitive. In both of these cases the Wassermann reaction was negative.

The Frei test is based on the development of allergy or hypersensitivity to the virus. This phenomenon has been thoroughly studied in numerous bacterial infections, particularly tuberculosis. Obviously, in the preparation of the antigen, as stated by Frei himself, it is of the utmost importance to use material from a definite case of lymphopathia venereum, in which other venereal diseases have been excluded, to make certain of bacteriological sterility, and to avoid overheating. Two reasons have been advanced in the literature to explain negative reactions in rare cases where there is every indication from the clinical picture to expect a positive test. The first is quite valid, that of anergy, or lack of allergy. That allergy varies, and even disappears, in all infections is well known. The second is that there may be two types of the virus of this disease with extremely slight clinical differences, but acting as separate antigens with individual allergy. (Hermans, Coutts.)

TREATMENT

In the treatment of lymphopathia venereum, numerous drugs have been used, including arsenic, antimony, manganese, and gold compounds. Antisyphilitic treatment has been shown to have no effect. Tartar emetic is most widely used, and while many observers have claimed good results, others have not met the same success. This drug acts as a specific in the treatment of granuloma inguinale, which probably explains the attempt to extend the use of tartar emetic to lymphopathia venereum. The confusion of these two diseases has been discussed. The great number of drugs that have been brought forth speaks for the unsatisfactory status of treatment.

Various authors have advocated daily intradermal injections of Frei antigen, or the intravenous injections of large doses of antigen. Still others have used the antigen as local applications.

Kalz and Sagher have used drugs, radiation, and immune serum, obtaining best results from the latter.

In the cases reported in this paper antisyphilitic therapy and tartar emetic had no apparent effect. High frequency fulguration (2 cases), X-ray (1 case), and malaria inoculata (given for another reason, 1 case) had no beneficial effects. Two patients with the least treatment showed the greatest healing.

It would seem that cure of lymphopathia venereum probably results only when the individual becomes immune to the virus. In no known virus disease is there a specific drug therapy. The transfer of passive immunity by injection of serum from individuals with healed lesions seems to offer the greatest possibilities in the treatment of this disease, although few studies of this method have been made.

SUMMARY

1. Eleven cases of disease of the urethra occurring in women are presented. The disease presents a syndrome—a chronic urethritis, with or without intra-urethral ulceration, which may remain extremely chronic and indolent or may proceed to urethral stricture, or to ulcerative destruction of the urethra; the ulceration may extend beneath the clitoris and labia, or about the introitus and deeply to the sides of the rectum; elephantiasis vulvæ may be associated.

2. The presence of positive Frei reactions in 9 of the 11 cases indicates that this syndrome is probably due to the virus of lymphopathia venereum—"lymphogranuloma inguinale."

3. A wide variety of parenteral and local treatment had no appreciable influence on the disease. Two patients with least treatment showed the greatest healing. The indications are that cure, as in other virus diseases, probably depends on immunity.

For helpful criticism, we are indebted to Drs. Thomas S. Cullen, Arnold R. Rich, and J. Earle Moore. For the drawings, we thank Mr. Jack B. Wilson.

NOTE.—Since this paper has been submitted for publication, 14 additional cases of this syndrome have been studied (13 negro women and 1 white). In 6 the Wassermann test was positive, and in all 14 the Frei test was positive.

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PLASTIC OPERATIONS FOR CONSTRUCTION OF AN ARTIFICIAL VAGINA

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ALTHOUGH fully five hundred cases of operation for construction of an artificial vagina have been reported in surgical literature of the world, no generally accepted method has as yet been described. The many techniques used fall into two main groups, namely, (1) those in which the lumen of the artificial vagina is lined with skin and mucous membrane introduced as free or pedicle grafts; and (2) those in which the vaginal canal is formed by a transplanted segment of the intestinal tract. Operations making use of skin and mucous membrane grafts are undeniably safer than intestinal transplantation, and apparently the end-results can be equally as good. Consequently, we believe that this second group of dangerous methods should be condemned and efforts directed toward improvement of the safer technique.

During the complicated embryonic development of the genital tract, the mullerian ducts may fail to fuse normally throughout all or portions of their lengths. The results of faulty or incomplete fusion are many and varied, and may involve fallopian tubes, uterus, or vagina alone, or any of these organs in combination. Usually when there is complete absence of the vagina, the external genitalia are normal, as are the ovaries and secondary sexual characteristics. The uterus may be absent or rudimentary, but occasionally is normal.

When the uterus is absent or physiologically inactive and there is no vaginal canal, these abnormalities often remain undiscovered until the patient marries or is examined to find the cause of amenorrhea. The discovery not infrequently produces a profound mental shock. To all appearances, she is a normal, healthy young woman. She has an abundance of the female sex hormone. She may have married or contemplated marriage with the expectation of assuming her full share of conjugal and family responsibilities. In such a case the construction of an artificial vagina should undoubtedly be attempted. But to what extent is the surgeon justified in hazarding his patient's life in order to provide for her an organ of coitus? In extreme cases when severe depressive psychoses are present, and even suicide threatened, extreme measures for relief, if they were necessary, might be considered. But when equally as good results can be obtained with the use of less dangerous procedures, unnecessary risks should not be taken.

We believe that the objections to the earlier skin grafting methods have been largely overcome. In the first place, such operations as those described by Frank and Geist, Graves, and Davis and Cron, are approaching closely the solution of the technical problem. Secondly, while the operative technique is of great importance, it has been learned that the postoperative management of the cases is of practically equal importance. The chief cause of failure in early operations of this type was scar formation and contracture which rapidly closed the lumen of the artificial vaginal canal. Dilatation is the solution to this difficulty. Dilatation should be begun early, repeated frequently, and prolonged indefinitely. Our first case, the report of which follows, illustrates strikingly the importance of dilatation in obtaining a good result. This operation was done by one of us—Dr. C. W. Flynn—in 1915, following the earliest and simplest technique of lining an excavation between the bladder and rectum with free grafts of skin and mucous membrane cut from the external genitalia. Dilatation was begun early by mechanical means, the patient married, and dilatation has been continued by natural means for a period of 19 years, during which time the artificial vagina has functioned perfectly as an organ of coitus.

Heppner, in 1872, first used skin from the labia and thighs to line an artificial vaginal canal. Scarring and contracture impaired the success of his attempts. To avoid this difficulty Baldwin, in 1904, suggested the formation of an artificial vagina from a double loop of small intestine or sigmoid brought down with its blood supply into an opening made between the bladder and rectum. He performed the first operation by this method in 1907, and the same operation was done independently by Mori of Japan about the same time. Schubert in 1911 modified Baldwin's method by detaching the rectum, moving it forward to be used as a vaginal canal, and bringing the sigmoid down to the anal orifice. These methods soon became popular, especially in Europe, and are at present preferred by many operators in spite of the operative mortality (variously estimated at

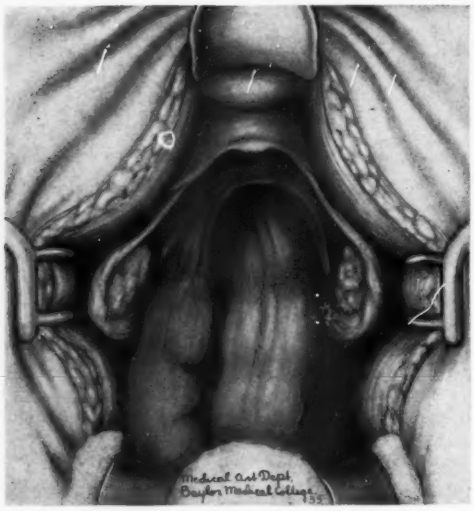

Fig. 1. Case 1. View of the pelvic organs showing the rudimentary uterus and tubes, normal ovaries, and pelvic kidney.

6 to 17 per cent) and not infrequent occurrence of serious complications such as cellulitis, peritonitis, incontinence, fistula, etc.

Returning to the safer skin grafting principle: Graves, in his textbook (1916), described an operation in which four pedicle flaps were used, two from the minor labia and two from the thighs, and sutured together and inverted into the space prepared between the bladder and rectum. It is difficult to obtain a vagina of sufficient depth by this method. What seems to us to be the best method so far described is that proposed by Frank and Geist in 1927. They used a single tubed pedicle flap from one thigh with delayed transfer which allowed them to obtain sufficient depth, and adequate blood supply to the graft was supplied while it was becoming established in its new location. They emphasized the necessity for early and adequate dilatation of the tube. The originators of this method have reported 4 cases and 1 each has been reported by Rushmore, Turrenne, and Grad. Our second case was done by this method, which makes 8 cases reported with uniformly good results and no deaths.

CASE 1. Patient, unmarried, aged 20 years, was admitted to the hospital August 31, 1915. The vagina was absent and she complained of cramping pains in the abdomen. The patient had been in excellent health and had developed normally during infancy and childhood. At 15 years of age she began to complain of frequent attacks of cramping pain on both sides of the lower abdomen. She began to have frequent headaches and complained of tiring easily. When at 16 years she had not menstruated, she was examined by the family physician who discovered the absence of a vagina. The abdominal pains gradually became less severe, but she continued to have headaches and was constantly nervous and irritable. About a month before the date of admission, the abdominal cramping returned, together with nausea, both of which persisted.

Fig. 2. Case 1. A schematic drawing of the pelvis and artificial vagina in sagittal section showing free grafts in place.

Physical examination revealed a well developed and well nourished young woman. The breasts were large and well formed, and there was normal female distribution of hair over the body. The external genitalia were normal. There was a hymen with a small slit-like opening, but inside, instead of a vagina there was only a blind pouch about 1 centimeter deep. By rectal examination, a small, tender mass could be felt in the location of the uterus.

Operation. Under general anesthesia, a low right rectus incision was made and the pelvic and abdominal cavities explored (Fig. 1). There was a small rudimentary uterus situated low in the pelvis. The fallopian tubes were present, but were contracted to mere fibrous cords in their proximal three-fourths. Both ovaries were normal in appearance, but the left was densely adherent to the posterior surface of the broad ligament. The right kidney was normal in size and location, but the left kidney was situated at the brim of the pelvis. Its ureter was proportionately short and its blood supply came from an artery leaving the aorta at its bifurcation. The appendix was irregularly thickened due to the presence of fecaliths in the lumen.

Since gestation was obviously impossible and there was a possibility of retention of menstrual products, the endomentrium-bearing portion of the uterus was removed, together with the left tube and adhered ovary. The appendix was also removed, and the incision closed.

The patient was then placed in the perineal position and a transverse incision made through the invaginated mucous membrane of the vaginal pouch. Through this incision the bladder and rectum were separated by careful blunt dissection until the peritoneum of the cul-de-sac was reached and the cervical stump of the uterus felt. The cavity thus formed was 10 to 12 centimeters in depth, and easily admitted three fingers. After all bleeding was controlled, the cavity was lined with free full thickness grafts of skin and mucous membrane obtained from the vulva (Fig. 2). The labia minora were completely excised and furnished the

Fig. 3. Case 2. View of the pelvic organs showing absence of uterus, rudimentary tubes, and normal ovaries.

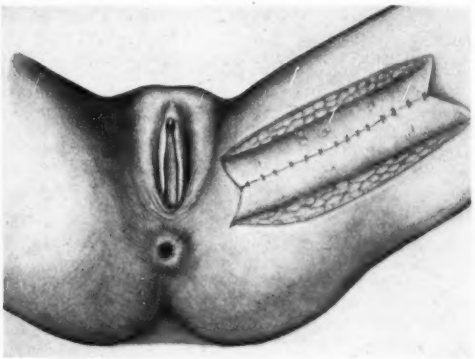

Fig. 4. Case 2. The tubed skin flap on the left thigh.

greater part of the grafted skin. The grafts were sutured loosely in place with fine plain catgut. A plug of rolled gauze, covered with rubber tissue and lubricated with vaseline, was inserted into the cavity to exert a constant uniform pressure upon the grafts.

The original plug was removed after 1 week. The grafts were inspected and all were found to be taking. The plug was replaced by a device designed to act as a constant dilator. This dilator was constructed of a large rubber bougie 10 centimeters long, mounted with a hinge-joint on a curved piece of metal which fitted against the symphysis pubis and the perineum, and was held in place by straps and a belt. This device was worn constantly night and day for 6 months except when it was removed once a day so that a cleansing douche could be taken. While healing was taking place, it was necessary to use silver nitrate to cauterize the granulations growing up between the grafts. Healing was complete with a minimum of scar tissue after about 6 weeks.

This patient was married 1 year after the operation. A communication from her husband dated August 24, 1934, states that the sexual relationship has been normal and entirely satisfactory to both husband and wife ever since their marriage. The vagina is 4½ inches deep. There is still a tendency for the lumen to contract when sexual intercourse is omitted for longer than 2 or 3 weeks, but there has never been any difficulty in dilating it.

Case 2. The patient was married, aged 18 years. She was admitted to the hospital April 24, 1933. Her complaints were: absence of menstruation; abnormality of genital organs; lower abdominal pain. The patient had been an apparently normal girl, and although she never menstruated, the breasts and other secondary sexual characteristics had developed normally. At intervals of 3 to 4 months during the past 3 years, she had dull pains in both lower quadrants, especially the right, and some backache. Otherwise there were no physical complaints. Six months ago she was married, and for the first time discovered that she had no vaginal orifice and normal sexual relations were impossible. On consulting a physician in the small community where she lived, she was told that there

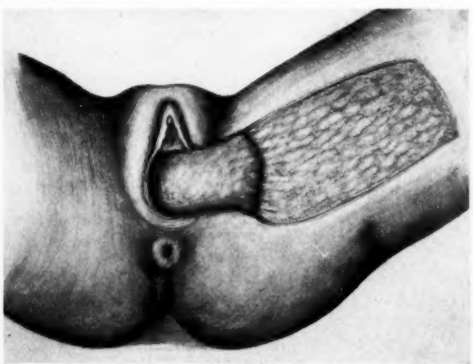

Fig. 5. Case 2. The distal pedicle of the flap has been severed and the free end transplanted into the space made in the loose tissue between rectum and bladder.

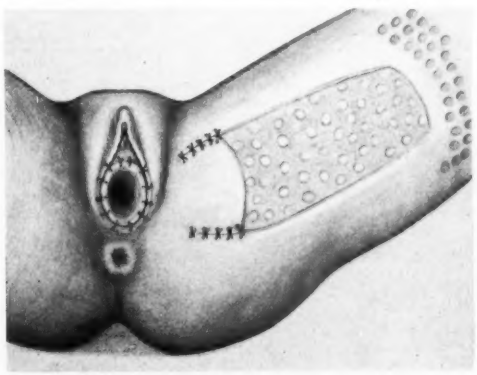

Fig. 6. Case 2. The proximal pedicle has been severed and returned to its original site. Small deep skin grafts are applied to the defect on the thigh. The tube graft is sutured in place.

was an absence of the vagina and uterus about which nothing could be done, and she and her husband were advised to have their marriage annulled. Not to be discouraged they sought other advice.

The patient was a robust, attractive young woman. No abnormalities were discovered except those of the pelvic organs. The external genitals were absolutely normal in appearance save for the one fact that a pliable membranous diaphragm completely closed the region where the vaginal orifice should have been. This had the appearance of an imperforate hymen. Rectal examination, however, revealed no evidence of the presence of a uterus or a vagina. A small mass high in the right side of the pelvis was thought to be an ovary.

The patient was anxious to submit to any surgical procedure which might offer a chance for correction of any part of her abnormality.

Operations. The first stage was done April 25, 1933. The first procedure was an exploratory laparotomy under general anesthesia, for the double purpose of discovering, if possible, the cause of her recurrent pain, and to determine whether any remnants of the uterus or vagina remained which might be used in the plastic restoration contemplated. This operation showed that the vagina was absent entirely and that the uterus was represented by only a thickened ridge extending upward on each side of the pelvis from the depths of the pelvic floor, and each ridge widening out at the brim of the pelvis into a much shortened fallopian tube with a normal fimbriated end. Both ovaries were located in their usual positions, and were normal in size and appearance (Fig. 3). The appendix was elongated, bound to the cecum with old adhesions, and contained several fecaliths. It was removed and the incision was closed. The patient was then placed in the perineal position and the first stage of an external plastic operation for artificial vagina was done. This consisted of partially raising a tubed skin flap from the inner side of the left thigh with proximal attachment at the edge of the labium major. This tube was about 8 inches long and 3½ inches in circumference (Fig. 4, method of Frank and Geist).

The second stage was done May 1, 1933, 6 days after first stage. The flap was completely undercut. Local anesthesia with novocain was used.

The third stage was done May 5, 1933, 10 days after the first stage, and consisted in cutting across the distal pedicle after testing with clamp (blanching of one-third).

The fourth stage was done May 17, 1933, 17 days after first stage. The pedicle was severed and closed. The free end was transplanted into the bed made in the loose tissue between the bladder and the rectum through a transverse curved incision in the hymenal diaphragm. The lumen of the tube was filled by a plug of vaseline gauze. A retention catheter was placed in the bladder (Fig. 5).

On May 22, 1933, the fifth stage was done, 27 days after the first stage. The cutting across of the proximal pedicle of tube was begun. The vaseline gauze plug was removed and the lumen of the tube was irrigated daily because of purulent exudate from the depths. A hard rubber dilator replaced the gauze pack.

On May 25, 1933, the sixth stage was done, 30 days after the first stage. The pedicle was severed and the base replaced in the original bed on the thigh. The remainder of the bed was grafted with small deep grafts (Fig. 6).

Patient was discharged June 2, 1933, 37 days after the first stage. No evidence of infection remained. The vaginal canal was 3 inches deep, and admitted two fingers.

A follow up, 6 months after operation, reported: Artificial vagina functioning satisfactorily to patient and husband. The dilator had been kept constantly in place, for 1 month then coitus begun, and the dilator was inserted twice daily.

A follow up, 18 months after operation, revealed that there had been some contracture of the inner end of the tube but the mucocutaneous junction had been drawn inward about 2 centimeters. The vagina still admitted two fingers to a depth of 3 inches. The mucocutaneous junction could be felt as a slight ridge. The skin of the tube was soft, pliable, and moist.

Although we are presenting Case 1 as an example of the excellent results which can be obtained by a simple operative method, we do not believe that the use of free grafts to line the cavity of the artificial vagina will be uniformly successful.

The employment of pedicle flaps as described by Graves, or preferably the tubed pedicle flap of Frank and Geist, will be much more likely to ensure healing with a minimum of scar tissue, and hence eliminate to a large extent the undesirable effects of contracture. Also, we wish to re-emphasize the great importance of adequate dilatation of the artificial lumen which must be begun early and continued indefinitely.

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THE OCCURRENCE OF DIFFERENT TYPES OF BRAIN TUMORS IN ONE PATIENT[1]

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WE are all familiar with the occurrence of different types of tumors in one and the same patient. Countless patients may have some form of benign tumor on the external surface of their body, fibromas, lipomas, and the like, and then develop a malignant tumor in some other portion of the body. Nobody, I believe, has ever taken particular notice of this fact or attached any importance to it. Then again, we have all seen cases in which a benign tumor, either due to trauma or some other irritation, has undergone malignant degeneration.

There are instances, however, in which multiple tumors occur in a patient; in these instances the evidence seems overwhelming that some fundamental condition exists in the organism which predisposes to tumor formation. I lack the special training to discuss the basic principles involved but would like to draw attention to several such cases that I have encountered in my service in the course of the past 15 years.

There are 4 such cases, of which I want to speak particularly.

The first one was a man who had an acoustic nerve tumor, of the von Recklinghausen type, which was removed by the intracapsular method 8 years ago. Until a month before admission, he had carried on his work as a railroad engineer without difficulty, when he developed symptoms of recurrence. At a second operation, there were found bilateral eighth nerve tumors, a recurrence at the original site having become enormous. He died after an attempted removal. Autopsy revealed five other tumors besides the two in the region of the eighth nerve. One of these was an osteoma and at least two others were meningiomas (Figs. 1 and 2).

The second case was a patient with an acoustic neuroma who died suddenly and had an unsuspected, enormous right frontal meningioma which had given no symptoms whatever.

The third case, which perhaps should not properly belong in this group and yet has points of similarity, is that of a woman on whom I removed, I thought completely, a meningioma compressing the cord. Fifteen years later she developed a recurrence at the same site. She had been free of symptoms for 14½ years.

The fourth case is one which I wish to report in greater detail. A boy of 17 years who all his life had the picture of a von Recklinghausen's disease with countless small tumors, some elevated and others merely the well known

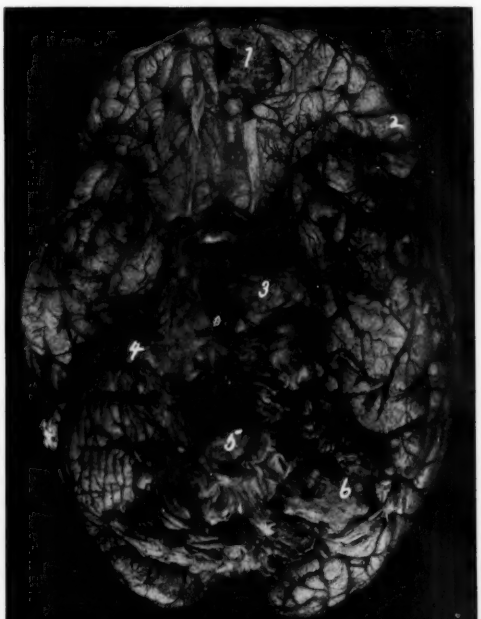

Fig. 1. *1*, Osteoma; *2* and *5*, meningiomas; *3*, *4*, and *6*, perineurial fibroblastomas.

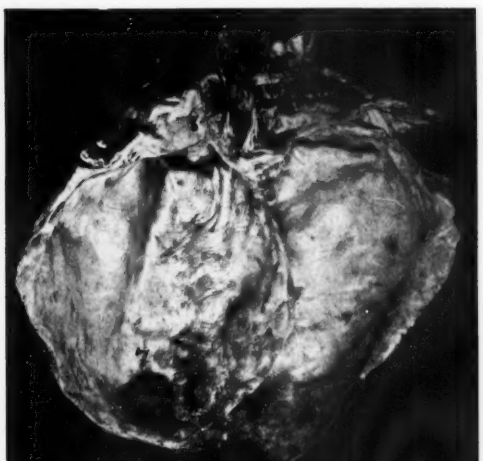

Fig. 2. This was the dura with two of the tumors attached; *7* and *8*, correspond to *2* and *5* seen in Figure 1—both meningiomas.

[1]Presented at the fifth congress of the Pan American Medical Association, March 1934.

Fig. 3.

Fig. 4.

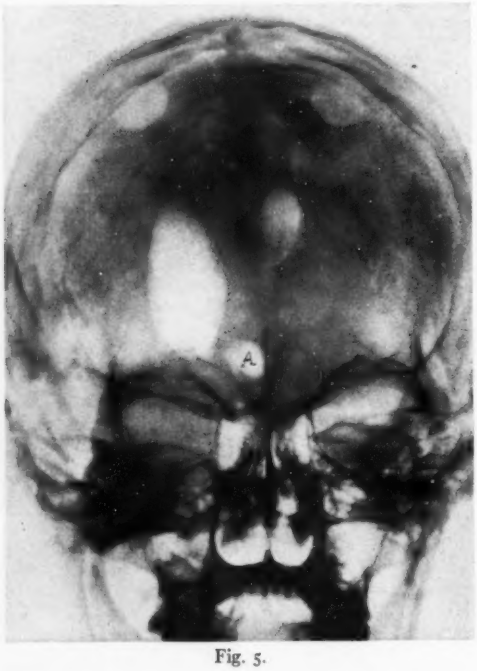

Fig. 5.

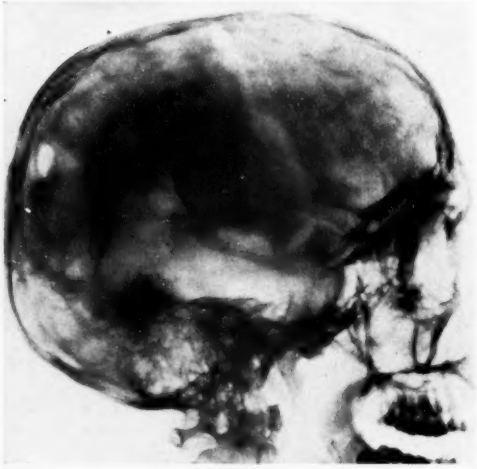

Fig. 6.

Figs. 3 and 4. Typical picture of von Recklinghausen's disease. The enlargement of the foot and the mass on the back are less usual in this disease.

Figs. 5 and 6. The collection of air at *A* (Fig. 5) in this view has the location but not the shape of the third ventricle. It is only in the lateral view (Fig. 6) that it is evident that the collection of air was a displaced lateral ventricle, which had been pushed over by the large cyst which occupied the entire right frontal lobe.

café au lait spots on his body. In addition, he had two large tumors, elephantiasis nervorum, one on his back and one on his foot (Figs. 3 and 4); also change in one tibia as has been described in von Recklinghausen's disease. This patient developed the symptoms of a brain tumor and, when admitted to the hospital, had a high grade of choked disc in both of his eyes, with a history of a recent loss of vision and, still more recently, a bilateral loss of hearing.

Examination suggested that we were dealing with a right frontal lobe lesion. An unusual series of air plates confirmed this idea (Figs. 5 and 6). At operation I removed a huge gliomatous cyst of the right frontal lobe, a typical astrocytoma, the cystic portion containing over 200 cubic centimeters of fluid and the solid portion weighing over 60 grams. The boy's hearing has improved markedly and all but the highest tones have completely returned. Evidently this loss of hearing was a pressure phenomenon and was not due to an actual destruction of the auditory mechanism.

The occurrence of different types of tumors in a patient with von Recklinghausen's disease has been reported before, but, in all instances that I am familiar with, the tumors have all belonged to the fibroblastic group. Here, however, is an instance of a tumor with an entirely different embryological origin. The accepted idea today in regard to astrocytomas is that they are a form of glioma and develop from the brain tissue itself. This case therefore raises two interesting points:

1. Does some condition exist in von Recklinghausen's disease which stimulates the growth of certain tissues in the body?

2. Does the particular type of glioma known as an astrocytoma belong to a different category and should we perhaps not include it in the glioma group, or does the unknown stimulating factor observed in von Recklinghausen's disease also affect other tissues than those of connective tissue origin?

UNDULANT (MALTA) FEVER OSTEOMYELITIS AND ARTHRITIS

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THE incidence of arthropathies and hydrarthroses complicating undulant fever is being and has been noted in the more recent medical literature. Bone lesions also have been observed but stressed very little. In the Ohio series of 175 cases of malta fever, Simpson finds 31 per cent arthropathies. In the Iowa series of 375 cases, Hardy quotes 32 per cent arthropathies, 1 case of hydrarthrosis and 1 of osteomyelitis. Baker reported an interesting case of intermittent hydrarthrosis. Weil has reported a case of hydrarthrosis of the foot due to malta fever and pointed out that this may occur either during the febrile period or long after its resolution. Zdrodowski reports 17.5 per cent bone or joint lesions occurring experimentally in guinea pigs inoculated with Brucella abortus. O'Donoghue recently reported a septic hip case due to Brucella melitensis, with pus formation which went on to bony ankylosis. Kulowski and Vinke were apparently the first to report an actual pus lesion occurring in the spine from which focus the brucella was recovered in culture.

Undulant fever is a general infection caused by one of the subspecies of Brucella melitensis. The natural habitat of these organisms is in the domestic animals, in which there is a widespread distribution. For man, the principal contact sources are cattle, goats, sheep, and swine. Undulant fever in man and infectious abortion in animals remained unrelated until Evans indicated in 1918 the close relationship existing between the organisms causing the two diseases. Although epidemics of infectious abortion in domestic animals have existed since the dawn of history, the causative organism was not discovered until 1895 by Bang and von Stribolt. In 1910 MacNeal and Keri isolated the specific organism from cattle in the United States. The first human case originating in the United States was reported in 1905 by Craig. In Iowa the disease is as prevalent as typhoid and paratyphoid according to Hardy who collected 1,430 cases in continental United States prior to 1929. The following classification of this organism has been suggested by Hardy, Jordon, Borts, and Hardy:

1. Brucella melitensis, variety melitensis.
2. Brucella melitensis, variety abortus (bovine).
3. Brucella melitensis, variety suis (porcine).

The most severe infections result from the melitensis variety. In Iowa it is believed that the abortus and suis varieties are equally responsible for the morbidity of undulant fever in man.

Human infection results from contact with infected animals through ingestion of raw dairy products or from handling live stock as fresh meat. The incubation period varies from 10 days to 3 weeks. The irregular multiform symptoms of the disease are well known, but it should be remembered that *cases presenting abscess formation may be expected to show a chronic continuous low grade temperature without periods of remission.* Of the greatest clinical importance have been the more recent reports of cases running a short course of a week or two. In these patients the condition might very easily be mistaken for influenza or a respiratory infection. The diagnosis is established by the agglutinin test, by skin tests, by blood culture, and by isolating the organisms from abscesses, from the urine, and sometimes from the stools.

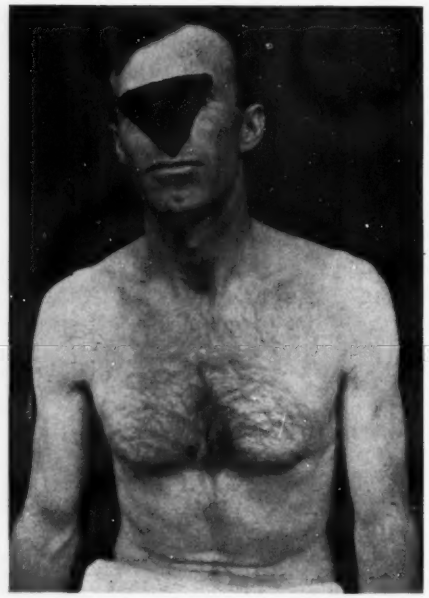

Fig. 1. Patient completely healed when last seen in April, 1934, and in good general health. No local or general subjective or objective symptoms. (Case 1.)

Fig. 2. Roentgenogram of humerus in 1934, showing the healed state of the lesion. There is nothing to distinguish this from an ordinary pyogenic osteomyelitis, except the tendency to loculation and rather mild general cortical, and absence of periosteal, reaction. The joint is not invaded. (Case 1.)

Perhaps malta fever involvement of the bones and joints is uncommon, but there is a certain satisfaction in making the diagnosis as in all unusual conditions. However, I feel strongly that in certain sections of the country many such specific infections are being overlooked chiefly because the possibility of malta fever is not thought of. There is another most important practical reason for making an accurate bacteriological diagnosis in this and other uncommon infections of bones and joints. Here especially secondary infection must be sedulously avoided. Malta fever is a self limited disease in most instances and proper drainage of localized abscesses will lead to cure. Secondary infection is a surgical disaster, prolongs the course of the disease and may threaten the integrity of the part affected or even the life of the patient.

The clinical material in this series comprises osseous and joint lesions in 5 adult males; 2 instances of spondylitis; 1 of a humerus; 1 wrist joint; and 1 instance involving the skull and ribs. Of these all but the humerus infection were diagnosed early as due to the brucella organism. The latter case was observed for almost 6 years before the real causative organism was suspected and recovered from the lesion. Three of the patients were employed about stock, one was a machinist, and the last a missionary who was infected in Africa. In only 3 of these cases did the systemic reaction lead to the suspicion of malta fever. Four were complicated by local suppurations which necessitated surgical drainage. One case of spondylitis did not suppurate and was finally healed by a bone graft fixation. Two of these were complicated by other lesions which led to some confusion in the differential diagnosis.

Because this series is relatively large there are several worthwhile points that warrant emphasis. Here, as in most acute infectious diseases, the osseous system is attacked rather late in the course of the disease. In 2 instances, however, these manifestations came on at the onset of trouble (Cases 1 and 3). In two instances local symptoms came on suddenly and in 2 cases rather insidiously. These manifestations were usually of a low grade nature and did not necessarily give rise to a constitutional reaction. Frank suppuration occurred twice, a seropurulent reaction in one and a non-suppurative lesion of the spine in which the bodies of the vertebræ were apparently attacked early (Case 2). The spondylitis lesion (Case 3) finally showed vertebral body invasion probably due to secondary invasion with the Staphylococcus aureus at a much later date. These suppurative lesions are amenable to surgical drainage and rest, the greatest care being exercised to prevent secondary infection (Orr method). The pathological inflammatory re-

ıctions are variable. Of the multiform bacterial causative organisms in pyogenic osteomyelitis and arthritis the Brucella melitensis must be given serious consideration.

CASE REPORTS

CASE 1. John S. (D7179), aged 37 years, a white American farmer, was first admitted to the hospital in August, 1928. A diagnosis of malta fever osteomyelitis of left humerus was made. The history indicated an insidious local onset with limitation of abduction of the left arm at the shoulder, of 4 years' duration and accompanied by moderate pain, of limited duration. There was no definite constitutional reaction. One year before his admission an abscess was incised over the left deltoid region which continued to drain until 4 months ago. Upon examination there was noted a small deltoid sinus and some induration and crepitation about the left shoulder joint with restriction of abduction due to muscle contracture. The X-ray picture revealed a quiescent cavity in the upper left humerus. No treatment was advised.

In April, 1932, he still complained of some pain about the affected shoulder. The pain radiated to the elbow. There had been no fever or other general reaction. There was 45 degrees of active and 70 degrees of passive abduction at the shoulder. In June, 1932, the lesion was operated upon and the brucella organism was recovered. The blood agglutination was also strongly positive. Recovery followed.

CASE 2. Lester K. (F1486), aged 22 years, a machinist, was admitted to the hospital in March, 1931. Diagnosis: malta fever spondylitis.

Patient's present illness dates back 6½ months at which time a diagnosis of malta fever was made by his attending physicians. His last fever episode had ended 1 month ago. About 2 weeks ago there first developed an insidious low back pain unaccompanied by any constitutional reaction or other general symptoms referable to his 6 months' old systemic infection. One week ago this symptom became very severe and forced the patient to bed. The pain was sharp, intermittent, radiated around the lower abdomen and was aggravated or provoked by any movements involving the spine. The patient looked ill and was in obvious pain, thus making the examination difficult.

On examination the abdomen was found somewhat tense and rigid. There was definite psoas muscle spasm. There was a slight low dorsal kyphosis, marked localized tenderness limited to the dorsolumbar region. There was pain on percussion and the spine was held rigid. There was definite muscle spasm. The root pains were aggravated on coughing. The liver was slightly ptosed but not enlarged. The spleen was not palpable.

Laboratory examination revealed: tuberculin tests, negative; urine, negative; hemoglobin, 93 per cent; red blood count, 4,960,000; white blood count, 6,500; and the sedimentation time, 55 minutes. Blood serum agglutination tests were strongly positive for malta fever in concentrations from 1:640 and 1:160.

The temperature curves were irregular for the several observation periods as follows: March, 1931, for a period of 3 weeks it was between 99 degrees and 101 degrees; June 1931, 99 degrees for 3 days; August, 1931, same for about 6 or 8 weeks; December and January, 1931, and 1932, for 5 weeks the temperature remained between 99 degrees and 100.5 degrees.

Recovery followed a course of conservative treatment which was fortified by spinal fusion in August, 1931. Three years later the patient was still symptom free.

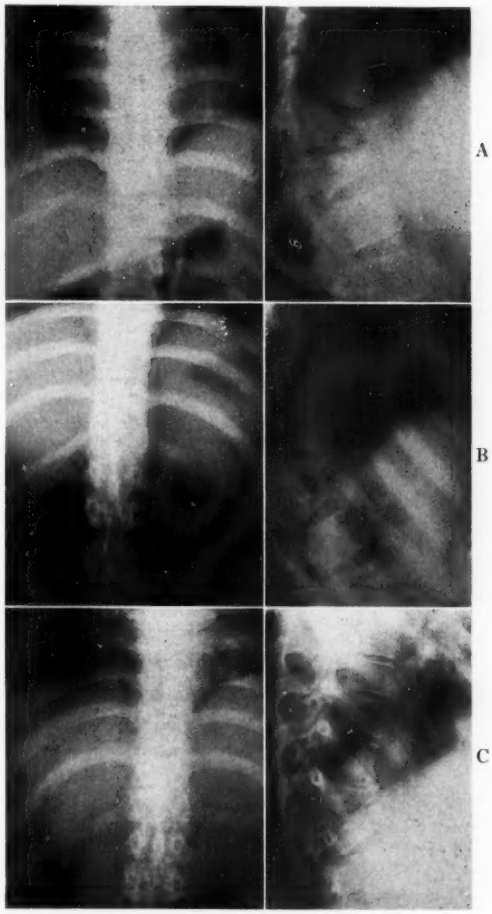

Fig. 3. A, March 19, 1931. Anteroposterior view of the lumbodorsal spine shows compression of the twelfth dorsal vertebra. There are no signs of abscess formation. The lateral view shows compression of the eleventh and twelfth dorsal vertebræ, with erosion of the anterior half of the twelfth superiorly which shows some reaction. This resembles fracture strongly but the disc is only slightly narrowed.

B, August 5, 1931. Now the disc is practically gone. There is osteophytic reaction above and below the site of the lesion. The erosive processes are much more pronounced. There is now no doubt that the lesion is of an inflammatory nature.

C, September 8, 1932. The anteroposterior roentgenogram shows increased condensation and still no evidence of abscess formation. The lateral roentgenogram shows definite gibbus formation and the bodies of the eleventh and twelfth dorsal vertebræ are beginning to fuse, as the disc is still more decreased. From the posterior aspect the graft appears to be adequately placed and to be solid. (Case 2.)

Fig. 4.

Fig. 5.

Fig. 4. The healed wound in December, 1932, after drainage operation by the Orr method. (Case 3.)

Fig. 5. Follow up X-ray examination after the patient had returned to the clinic with a return of the low back symptoms, on August 21, 1933. Now the psoas shadow shows a definite bulging on the left, indicative of abscess formation. The disc between the fourth and fifth lumbar vertebræ is slightly narrowed and in the anteroposterior views there are slight proliferative changes not so evident in the lateral plates. This proved to be due to the secondary invasion by the staphylococcus which was recovered in pure culture from the abscess at operation. (Case 3.)

CASE 3. (Reported in detail by Kulowski and Vinke). Robert D., aged 33 years, a white American farmer, married, was admitted to the hospital March 5, 1932. Diagnosis: malta fever spondylitis.

The patient stated that he was in excellent health until August, at which time he developed low back pain which came on insidiously. This was dull and aching in character and had no relation to his physical activities in particular. The pain did not radiate and was more or less constantly present. He continued performing his daily routine until 2 weeks before admission, when the pain became so severe that he was forced to seek relief by recumbency and analgesics. He was getting progressively weaker.

On examination, the patient was found to be a well developed and well nourished man weighing 184 pounds, 5 feet 11 inches tall, with a moderately flushed face, in obvious pain, not dyspneic, and lying quietly in bed. The abdomen was normal in contour and muscular tone. The liver was barely palpable below the right costal margin; the spleen was just palpable. There was tenderness on palpation over the lower lumbar region a little to the right of the midline. There was spasm of the erector spinæ mass over the same area. Motions of the lumbar spine were limited. The sacro-iliac and hip joints were not remarkable. There was no abdominal muscle spasm, but a definite localized area of increased temperature of skin of right lower quadrant, of which patient himself was conscious.

Roentgen examination of the pelvis and hips did not show any pathological changes of the bone. There were destructive changes in the interarticular facets of the lower lumbar vertebræ on the right, most pronounced between those of the fourth and the fifth. The psoas shadow was distorted on the right side; it ballooned out inferiorly, suggesting abscess formation. The lateral views of the spine were essentially normal.

The epidemiological data showed that the patient had had contact with cows and hogs and had been exposed to raw dairy products.

Drainage of a huge prevertebral abscess through a posterior route was followed by a comparative uneventful recovery. The brucella was recovered from the pus. The wound healed after several months. About 1 year later he returned again complaining of low back pain. Physical and X-ray examination revealed a left psoas abscess. This was drained through a left Royle type of incision and a large abscess was evacuated. Remarkably enough a pure culture of staphylococcus was recovered in culture and no more evidence of brucella infection was found although careful cultural efforts to detect its presence were made repeatedly. The patient made a good recovery and is now apparently free of all symptoms. A secondary bacterial invader was the cause of the recurrence of the lesion. Following invasion by the staphylococcus there were gross X-ray changes of a hypertrophic nature, characteristic of pyogenic spondylitis.

CASE 4. Ivo G. (G6089), aged 32 years, stock buyer, was admitted to the hospital in December, 1932. Diagnosis: malta fever arthritis of the wrist joint.

The patient's illness dates back 6 months before his admission to the hospital. His symptoms came on suddenly with a constitutional reaction. His blood serum, sent to the University Hospitals, exhibited positive agglutination tests for malta fever in a dilution of 1:640. He remained in bed for 2 months and in September there was a sudden onset of aching in the left wrist which became sharp and piercing.

The examination revealed a well developed and well nourished adult male who did not appear to be generally ill. The left wrist presented a fusiform swelling chiefly on the dorsal side which was generally tender. The dorsum suggested some fluctuation. The skin over the wrist was warm and reddened. The entire hand was swollen moderately. All motions of the hand and wrist were painful.

Laboratory examinations of the blood and urine were normal. Wassermann was negative. Agglutination for typhoid and paratyphoid was negative. The blood serum agglutination for malta fever was positive up to a dilution of 1:160. For the porcine variety this goes up as high as 1:50,000.

The wrist was drained and a small amount of seropurulent material evacuated from the radiocarpal joint. The lateral half of the semilunar carpal bone was roughened and sclerotic and somewhat loose. This was removed. A

similar condition presented in the contact surface of the scaphoid bone. The result was recovery with some limitation of wrist motion.

CASE 5. (No. 28589). The patient, a missionary, aged 43 years, was admitted to the hospital in January, 1934. Diagnosis: malta fever skull and ribs.

The patient developed malta fever while in Africa in May, 1931. At the end of a month an abscess developed over the ribs anteriorly. In August, 1931, while he was on the boat returning to his home, an abscess was drained over the right hip. This drained for 10 weeks while he remained in England. All drainage then ceased until September, 1932, when this recurred and persisted for 1 month and again recurred for a brief period in December. Since then he has been free of pain except for an occasional pain and some tenderness in this region. In October, 1931, the fourth and fifth ribs became enlarged and were widely drained in February, 1932, which subsequently drained for 6 to 8 months and finally healed after a course of arsphenamine and potassium iodide. He got along fine until he developed a skull lesion in September, 1933. This was drained and the pus was culturally sterile. He believes that he developed a secondary infection in December as the X-ray pictures then showed bone involvement. At this time Staphylococcus aureus was recovered from the head wound. He has gained weight and has had some low back pain ever since the onset of his illness.

On physical examination the positive findings were: tenderness over the right sacro-iliac joint, and there were several healed scars about the hip joint and one over the skull.

The Wassermann reaction and agglutination tests for undulant fever were negative at this time.

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FIVE AND TEN YEAR END-RESULTS OF THE TREATMENT OF CANCER OF THE CERVIX UTERI BY IRRADIATION

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FROM 1913 to 1929, inclusive, 955 cases of epidermoid carcinoma of the cervix uteri were examined at the State Institute for the Study of Malignant Diseases. Eighteen cases were not treated; 937 were treated by irradiation.

In presenting such a large series, in order to convey the significance of the result of treatment to those interested, it is necessary to classify the cases in some manner.

Numerous observers have endeavored to prognosticate results and group cases by means of grading the biopsy specimens. This should not be overemphasized, but, taken into consideration with the amount of anatomical involvement, it has, we believe, a distinct scientific value. However, to prognosticate on the histology alone does not seem warranted. Norris (11) in speaking of this method says: "Histologic examination is neither a very practical nor a reliable guide as to either the prognosis or the radiation dosage. It may be of some use in groups, but means little in the individual case." Jorstad and Auer say, "From an analysis of the grading of all the cervical cancers treated by radium from 1917 to 1927 (Barnard Free Skin and Cancer Hospital), it can be concluded that grading alone is of no prognostic value."

We are still of the opinion that grouping cases according to anatomical involvement and the clinical manifestations is more reliable in making a prognosis in the individual case than the histological grading of biopsy specimens alone, as so many factors enter into the obtainment of a good result. Accordingly, we have adopted the Schmitz classification, and since 1920 we have grouped each case at the time of treatment. And, although it is undeniable that a personal equation enters into this grouping of cases, we believe it affords a working basis for comparative statistical results.

Thirty-eight, or 3.9 per cent of our 955 cases, fell into group I; 61, or 6.3 per cent, into group II; 274, or 28.6 per cent, into group III; 456, or 47.7 per cent, into group IV. The cases received which were recurrent after hysterectomy were placed in a fifth group and 117, or 12.2 per cent, fell into this group; 9, or 0.9 per cent of the cases, were treated prophylactically after hysterectomy.

Nearly all of the cases were treated by external irradiation followed by intra-uterine radium as described in a previous paper (15). The results of treatment are given in Tables I and II.

In this report no case is included in which there was any doubt as to the malignancy. After the biopsy, the so called doubtful cases of histological malignancy have been eliminated entirely.

In reviewing the number of cases presented here we would like to call attention to the fact that these cases, as classified, show only 10.3 per cent of the cases in groups I and II, the cases which might be considered in the operable group; that the advanced cases are in the majority; 28.6 per cent fell into group III; 47.7 per cent into group IV, the hopeless cases.

Table III shows a comparison of the type of cases received at the Institute with the types received at other clinics, as reported by various investigators. The percentage of group IV cases in our series is considerably higher than from other clinics.

The large number of group IV cases may be explained on the basis that the physicians throughout the State of New York, outside of New York City, refer these cases to the Institute while many of the more favorable ones are treated in other clinics. The policy of the Institute has been to accept patients for whatever palliation or comfort might be obtained from treatment but ordinarily, we believe a great majority of them should have been refused treatment, for in this advanced group, 64.8 per cent of the 447 cases treated, died within the first year; 42.5 per cent of the 447 died within the first 6 months. Yet, all the cases were included in this statistical report.

At present it seems the consensus is that the result of treatment should be determined from the percentage of survivals of the total cases seen, and we also are submitting our report in this manner.

As compared with the absolute statistics (Table IV) from other clinics it will readily be seen that on analysis our percentage of survivals in the first three groups compare very favorably with the results of any of the large cancer clinics. However, the inclusion of the large number of group IV cases makes the aggregate statistical result somewhat lower for our clinic.

As all investigators are agreed that there is little salvage in the group IV cases, it would seem

TABLE I.—FIVE YEAR END-RESULTS[1] OF TREATMENT

Group	Number of cases examined	Number of cases treated	Five year survivals			Five year healings (cured cases)		
			No. cases survived	Per cent absolute survivals	Per cent relative survivals	No. cases healed	Per cent absolute healings	Per cent relative healings
I	38	37	26	68.4	70.0	24	63.1	64.8
II	61	61	21	34.4	34.4	20	32.7	32.7
III	274	268	55	20.0	20.5	49	17.8	18.28
IV	456	447	7	1.5	1.5	5	1.0	1.1
V	117	115	12	10.2	10.4	12	10.2	10.4
Prophylactic	9	9	3	33.3	33.3	3	33.3	33.3
Totals	955	937	124	12.9	13.0	113	11.8	12.

[1]All cases lost from observation or dead from intercurrent disease are counted as dead from the disease.

TABLE II.—TEN YEAR END-RESULTS[1] OF TREATMENT

Group	Number of cases examined	Number of cases treated	Ten year survivals			Ten year healings (cured cases)		
			No. cases survived	Per cent absolute survivals	Per cent relative survivals	No. cases healed	Per cent absolute healings	Per cent relative healings
I	18	18	8	44.4	44.4	7	38.8	38.8
II	39	39	9	23.0	23.0	9	23.0	23.0
III	163	159	13	7.9	8.1	13	7.9	8.1
IV	260	253	0	0	0	0	0	0
V	74	74	10	13.5	13.5	10	13.5	13.5
Prophylactic	6	6	1	16.6	16.6	1	16.6	16.6
Totals	560	549	41	7.3	7.4	40	7.1	7.2

Two of the 18 patients in group I were clinically well for 5 years and 1 was clinically well for 7 years when they died from intercurrent disease with no evidence of malignancy at the time of death.

One of the patients in group II was clinically well 9 years and 2 months when she died from intercurrent disease.

Six of the cases in group III passed the 5 year period without any evidence of the disease; 3 died from intercurrent disease, 1 after being clinically well for 7 years and 2 after being clinically well for 5 years; 2 died from recurrence of their malignancy, 1 after being well for 9 years and 1 after being well for 5 years; 1 patient was lost from observation after being clinically well for 8 years.

[1]All patients lost from observation or dead from intercurrent disease are counted as dead from the disease.

TABLE III.—A COMPARISON OF THE TYPES OF CASES RECEIVED IN DIFFERENT CLINICS AS REPORTED BY VARIOUS INVESTIGATORS

Classification	Investigator	Per cent group I	Per cent group II	Per cent group III	Per cent group IV	Per cent group V	Per cent prophylactic
Schmitz	Ward and Sackett (21)—457 cases	2.	18.6	69.3	10.1		
	Norris (12)—153 cases	18.9	12.4	37.9	30.7		
	Schmitz (14)—488 cases	7.1	12.7	45.4	34.6		
	Schreiner and Wehr—955 cases	3.9	6.3	28.6	47.7	12.	0.9
Individual	Burnam (3)—1578 cases	9.37		61.40 plus 6.27 palliative		10.13	3.8
League of Nations	Crossen and Newell (4)—121 cases	2.4	9.	80.1	8.2		
	Lacassagne (10)—350 cases	10.8	37.7	42.5	8.8		
	Heyman (6)—1439 cases	9.8	28.	38.7	23.5		
	Voltz (20)—2202 cases	16.8	22.2	36.1	24.7		
	Ward and Sackett (21)—457 cases	20.6	39.2	30.1	10.1		
American College Surgeons	Bartlett and Smith (2)—143 cases (Cases traceable for 5 years)	3.49	7.62	48.2	40.5		

TABLE IV.—COMPARATIVE FIVE YEAR END-RESULTS OF IRRADIATION TREATMENT OF CARCINOMA OF THE CERVIX UTERI

Classification	Investigator	Percentage of survivals or cures							
		Group I	Group II	Group III	Group IV	Group V	Prophylactic	Total salvage all cases	Total salvage from groups I, II, & III
Schmitz	Ward and Sackett (21)—457 cases Survivals	66.6	50.6	19.6	0			24.29	27.
	Norris (12) —153 cases Cures	44.8	26.3	20.6	10.6			22.8	28.3
	Schmitz (14)—488 cases Good end-results	80.	41.94	16.36	1.72			19.14	28.2
	Schreiner and Wehr—955 cases Cures Survivals	63.1	32.7	17.8	1.0	10.2	33.3	11.8	24.9 27.3
Individual	Burnam (3)—1578 cases Cures	54.73		11.35		11.25	41.66	15.96	.....
League of Nations	Crossen and Newell (4)—121 cases Survivals	....	....	....	....			23.9	26.1
	Lacassagne (10)—350 cases Cures	42.	28.	10.	0			20.0	21.0
	*Heyman (6)—1439 cases Cure rate—relative absolute—1537 cases	57.5	34.3	16.2	5.3			21.9 21.3	28.06
	*Voltz (20)—2039 cases Cures—relative absolute—2202 cases	45.1	24.1	12.9	0.4			19.4 17.6	20.9
American College Surgeons	*Bartlett and Smith (2)—143 cases Five year survivals for traceable cases	80.	27.3	11.6	3.5			11.9	

*Except for these last three investigators, the figures given are absolute.

that the thing to do would be to calculate the percentage of survivals from the first three groups for comparative results.

It will be plain to the reader of this statistical paper that results in a curative way by irradiation treatment of cancer of the cervix, will be improved only when these lesions are discovered in the incipient stage when the treatment is quite satisfactory. This will be accomplished only as the knowledge which has been gathered by students of cancer can be disseminated among the lay people as well as among the general practitioners of medicine.

This necessitates periodic health examinations which include a complete physical examination and, in this particular field, careful bimanual pelvic examination together with inspection of the vagina and cervix with a good light, preferably with the colposcope. The use of Lugol solution as advocated by Schiller is of value in detecting areas which are suspicious of malignancy. The areas which do not stain should be selected for biopsy, as after all, biopsy is the most important thing in a questionable case.

Emmert, upon reviewing the case histories of patients with advanced disease, found "that one-half of the patients claimed they had been under the care of a physician for periods of time ranging from 2 months to 1½ years, during which time the signs of early malignancy were not recognized."

The important steps in cancer prevention are, we believe:

1. The full appreciation of the importance of a periodic health examination which will disclose inflammatory lesions such as cervicitis and erosion, the results of infections and chronic irritations in the endocervix, and the proper treatment of these by means of operative interference and cauterization. Bailey, in his researches which are worthy of careful consideration by all who are endeavoring to prevent malignancy, states that the ultimate sequel to erosion is malignancy.

2. The proper and careful attention during pregnancy, delivery, and puerperium to prevent lacerations and infections. In our 955 cases only 21 were unmarried women, 97 were nulliparous and in the remainder pregnancies or miscarriages are recorded from one to eighteen times. It is very evident from this fact alone that child bearing with its resulting trauma and the cervicitis (inflammation of cervical glands), in other words, chronic inflammations, is a distinct factor in the etiology of cancer of the cervix.

TABLE V.—AGES

Age in years	No. Cases	Per cent in each age period
20 to 24	8	0.8
25 to 29	30	3.1
30 to 34	63	6.6
35 to 39	94	9.8
40 to 44	146	15.2
45 to 49	151	15.8
50 to 54	155	16.2
55 to 59	150	15.8
60 to 64	81	8.5
65 to 69	46	4.8
70 to 74	21	2.2
75 to 79	7	0.7
80 to 83	3	0.3
Total	955	....

Attention is frequently called to the fact that the incidence of cervical cancer is lower in Jewesses. Sorsby says: "The observance of the Mosaic code undoubtedly produces a high degree of sexual cleanliness; and it is suggested that this cleanliness, with its concomitant restrictions on cohabitation at times when rest is probably beneficial, as after parturition and menstruation, is a factor in the lower incidence of uterine cancer among Jewish women—the regulations of the Mosaic code make the appearance of discharges a cause for inquiry as to its nature and a woman with a blood-stained discharge is theologically 'unclean.'" Only one of the patients in our group was Jewish.

Kaplan, in reporting the cases examined at the Bellevue Hospital in New York City, says that only 4 per cent of his series were Jewish.

3. A realization of the possible dangers that may result from the use of strong chemicals, drugs, instruments, and instrumentation, sometimes used as contraceptives.

Parabuceu, quoted by Stout, collected data from several Russian gynecological clinics which show that cancer of the uterus in women from 24 to 30 represents no less than 24 per cent of all cases of uterine cancer. He attributes this to the increasing use of artificial abortion and anticonceptional methods in Russia.

4. A full realization that cancer of the cervix may occur at any age period in life as is indicated in reviewing the age table (Table V).

From this table it will be seen that cancer of the cervix has occurred in every period in adult life, the youngest being 20 and the oldest being 83; that there is a gradual and perceptible increase in the percentages in each 5 year period up to the maximum of 55, and then a decline. In our series (16) 4.9 per cent occurred at age 30 or younger. Johnson and Tyrone report 6.5 per cent under the age of 30.

The duration of symptoms for our cases was about the same for all groups, from a few weeks to several years; 632, or 66.1 per cent of the patients, complained of bleeding as their first symptom; 126, or 13.1 per cent, of a discharge, either watery, yellowish, leucorrheic, or greenish; 123, or 12.6 per cent, as a watery discharge which later became bloody; 53 of pain or pressure symptoms with no discharge; 7 were discovered on routine physical examination; 14 gave indefinite histories. Pain accompanying symptoms was found in the advanced cases. From this, we conclude that there is not much to be learned of the extent of the disease from the symptoms.

Abnormalities of the menstrual function, prior to the beginning of the present complaint, were found in only 159 of the cases; 102 patients reported painful periods; 30 irregular periods; 23 irregular and painful periods; 3 severe headaches; and 1 patient reported irregular periods and nose bleeds.

Ninety-five, or 9.9 per cent, of these women gave positive Wassermann reactions. Touraine, in the study of 29 cases of leucoplacia of the cervix in which syphilis was present clinically in 66 per cent, found 12, or 41 per cent, terminated in epithelioma.

Nothing of any consequence was learned from a study of the nationality in our series, except that there was only one Jewess among 955 patients.

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EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

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APRIL, 1936

WILLIAM H. WILMER

WITH sorrow the Editorial Staff of SURGERY, GYNECOLOGY AND OBSTETRICS has learned of the death of one of its most honored members, Dr. William H. Wilmer.

As a surgeon, a leader in the field of ophthalmology, and a citizen, he has long been a distinguished figure in American life. Dr. Wilmer's career was characterized by many fruitful accomplishments. In a subsequent number the Journal will give more adequate recognition to his achievements.

THE SURGEON'S DEBT TO FUNDAMENTAL SCIENCE

THE time is not far removed when a surgeon achieved eminence by the development of brilliant, dexterous, and rapid technical procedures during an operation. While such skill must still be an asset to the surgeon, yet if not accompanied by the knowledge and appreciation of the biochemical, physiological, and psychological disturbances inseparable from all disease processes, the results of such surgical procedures will leave much to be desired. Such an individual is merely an operator, a technician, carrying out stereotyped procedures—not a surgeon.

The training of a surgeon has now become so complicated that the former presumably adequate knowledge of anatomy and surgical pathology must be supplemented by a training in biochemistry and physiology. To these sciences we are deeply indebted.

If obstruction occurs in any hollow tube of the human organism, the resultant disaster in all instances is hastened by the associated biochemical upset. A dexterous but precipitate operation to relieve an obstruction in the small bowel, colon, common bile duct, ureter, or urethra will result in a discouraging mortality if the biochemical disturbances are neglected and left untreated as shown by the knowledge provided through research experiments conducted by the fundamental sciences.

How often a precipitate operation in a septic patient ends fatally. The patient may be overcoming the initial focus and localizing it as a relatively innocuous abscess, but most frequently the price of such a victory is exhaustion from pain and sleeplessness, dehydration, and a change in ratio of circulatory fluids, salts, and solids, the net result being an organism with a completely disturbed metabolism and an embarrassed circulation.

If the associated disturbances are corrected before an operation is undertaken, the de-

lightful improvement of patients suffering from the lesions mentioned is well-nigh incredible. The most obvious and easily corrected are pain and dehydration, with the inevitable disturbance of the acid base balance. The intravenous administration of saline and glucose in large quantities, often thousands and not hundreds of cubic centimeters, is required to restore the balance of the circulatory fluids. Morphia gives mental and physical rest.

When the improvement in the patient's condition has reached a stage where an operation is possible, it should be of the most simple character, dealing solely with the lesion responsible for the disability. From the physiological and biochemical laboratories has come evidence of the necessity of decompression of a distended viscus prior to any extensive operative procedure. Examples of the practical application of the above principle are found in a cecostomy for obstruction due to cancer of the colon, a cholecystostomy or draining of the common bile duct in empyema of the gall bladder or cholangitis, or decompression of the urinary bladder when urethral obstruction follows prostatic enlargement. Such procedures are not directed to the correction of the actual organic lesion causing the disability: they are directed to correcting the physiological and biochemical upsets resulting from such a lesion. By these minor procedures the patient is rescued from a severe crisis, and the radical procedure necessary to attack the primary organic lesion may be carried out with safety at a later date. It would be disastrous to do a radical operation on a patient for a cancer of the colon, when the patient really is suffering from intestinal obstruction.

The application of the above principles to patients suffering from acute perforation of a duodenal ulcer has permitted us to operate on forty consecutive patients without a death. Sixteen of these patients required subsequent radical operation. None died from this secondary procedure. The time consumed in carrying out such pre-operative preparation is more than justified by the ultimate results.

For this attitude to clinical problems we are indebted to the fundamental sciences. The more "biologically minded" a surgeon becomes, the lower will be his mortality; the less will his patients suffer mental and physical anguish during and subsequent to their surgical therapy. ROSCOE R. GRAHAM.

PERITONITIS FOLLOWING COLONIC SURGERY

USUALLY peritonitis following intestinal operations is attributed to (1) contamination at the time of the surgical procedure, or (2) infection which develops subsequently because of impairment of the vascular supply of the segment of bowel. While improvement in operative technique has unquestionably diminished the occurrence of peritonitis, it nevertheless still remains one of the outstanding postoperative complications of abdominal surgery.

Peritoneal infection may be expected if, at operation, contamination of gross character has taken place, but when it occurs following a surgical procedure in which there has been no soiling and no obvious technical error, it is a tragedy. Older contemporary surgeons have observed repeatedly that peritonitis develops with comparative rarity following secondary abdominal operations, provided the primary procedure has been carried out only 2 or 3 weeks previously. For example, peritonitis is quite uncommon following closure of a colonic stoma subsequent to segmental resection of the colon, and the conjecture is made that its failure to develop is due to immunization that has been brought about by the primary opera-

tion and the presence of the stoma. If this statement even in part is correct, the feasibility of attempting immunization against peritonitis arises.

Some feel that the use of vaccine in an attempt to prevent peritonitis following colonic operations is useless; others believe that it is dangerous. Progress in medicine must be made cautiously and slowly, but many find it difficult to accept any new idea simply because it deviates from the paths of tradition. The attempt to vaccinate patients who are to undergo operation on the colon is not new in principle; Mikulicz attempted it many years ago. The vaccine he used contained colon bacilli which had been killed. The occurrence of some severe reactions discouraged him and he discontinued the use of the vaccine. During the past 2 or 3 years Gosset has administered vaccine subcutaneously prior to abdominal operation in an effort to decrease the incidence of peritonitis, and he is of the opinion that it is of considerable value. The work of Steinberg and Goldblatt also lends evidence to the contention that vaccination is apparently a preventive therapeutic measure against infections of the peritoneum.

In the past 7 years more than 2,500 intraperitoneal injections of vaccine have been made at the Mayo Clinic as a preventive measure against peritonitis in cases requiring intestinal operations. The vaccine is made from killed streptococci and colon bacilli. The amount of vaccine usually employed in each case was 1 cubic centimeter (500,000,000 organisms) in 10 cubic centimeters of physiologic saline solution as a diluent. However, for patients of small stature and for children, smaller doses were administered. Vaccination is carried out by means of a long, spinal puncture needle after the abdominal site has been carefully prepared and the area anesthetized by the use of procaine. In addition to the vaccine, which is given 48 to 60 hours prior to operation, all patients are hospitalized for 3 to 5 days before operation. During this period an effort is made to cleanse the bowel as thoroughly as possible without increasing the debilitation of the patient. Stated briefly, the procedure consists in the employment of a diet high in carbohydrate and the use of mild saline cathartics. If the bowel is obstructed or nearly obstructed, warm saline irrigations are substituted for cathartics. All of the 2,500 patients who were given the vaccine underwent some type of intestinal operation subsequently, and in the interim since the institution of this plan of pre-operative preparation, the mortality from peritonitis following intestinal surgery has decreased 66 per cent.

According to recent experience, it would seem that the dangers of intraperitoneal vaccination can best be summarized by stating that there has not been an alarming reaction or death that could be attributed to the use of the vaccine. Intraperitoneal vaccination is not projected as a sure preventive against infection, but the principle is fundamentally sound and the employment of the vaccine seems to be a step in the right direction.

CLAUDE F. DIXON.

LANDMARKS IN SURGERY

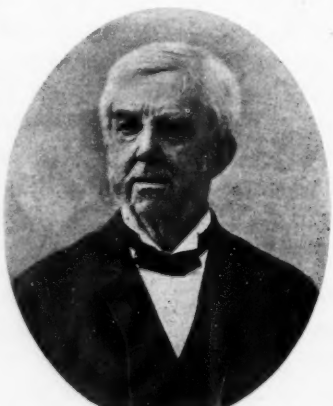
OLIVER WENDELL HOLMES AND PUERPERAL FEVER

J. P. GREENHILL, M.D., F.A.C.S., CHICAGO, ILLINOIS
Professor of Gynecology, Loyola University Medical School

IT rarely happens that a man is fortunate enough to acquire merited distinction in two entirely unrelated fields of human endeavor. A physician who acquired this distinction is Oliver Wendell Holmes. The average American layman thinks of Oliver Wendell Holmes as the author of a wide variety of literary gems, especially the *Autocrat of the Breakfast Table.* Most Americans do not know that Holmes was a physician and a professor of anatomy for 35 years. However, as Holmes himself said, he made far greater contribution to humanity as a physician than as an author and poet. Many physicians have become literati, but, as Osler pointed out, they did so at the expense of acquiring distinction in the field of medicine. Holmes was a rare exception, for he became famous both in medicine and in literature.

Oliver Wendell Holmes did not start his educational career studying medicine. Instead he began the study of law at the Harvard Law School but after one year he gave this up and turned to medicine. After graduating from medical school he went abroad where he came under the influence of a number of prominent teachers. Bearing in mind the famous French physician Louis, he said, "I have fully learned three principles since I have been in Paris, not to take authority when I can have facts; not to guess when I can know; not to think a man must take physic because he is sick." Throughout his entire life Holmes never forgot these three principles.

After his return to America Holmes began the practice of medicine; but if the number of patients he had and the income he derived from them are used as criteria, Holmes was not a successful physician. He knew this better than any one else and as he himself said, "A man who writes poetic ditties must not write prescriptions. To be a wit was bad enough; to be a poet, worse. Better be a rascal or hard drinker and have some bond of sympathy with your few patients." However, Holmes was eminently successful from every point of view as a teacher. For 35 years Holmes was professor of anatomy at the Harvard Medical School. In the early years Holmes taught not only anatomy but also physiology and he had so many duties to perform that he was led to make the following oft-repeated statement, "Instead of filling a chair at the University, I really occupy a settee." Although the teaching of anatomy is difficult to make interesting and although Holmes' lectures were given at the time of day when most students were fatigued, the students were always eager to attend these lectures. Holmes was famous as the greatest conversationalist in America, for he talked better than he wrote. He had a delightful sense of humor, and this, coupled with his extensive knowledge of anatomy and his familiarity with the history of the great anatomists, made Holmes' lectures inspiring. Holmes was always interested in old books on medicine and collected a large number of them which are now in the Boston Medical Library. It may also be of interest to know that Holmes wrote the greatest number of poems dealing with medical subjects in the English language. Among these are such well known poems as "Rip Van Winkle, M.D." and "The Stethoscope Song."



Oliver Wendell Holmes
1809–1894

In 1843 Holmes read a paper on "The Contagiousness of Puerperal Fever," before the Boston Society for Medical Improvement. This paper was published in the *New England Quarterly Journal of Medicine and Surgery* in April, 1843, but it aroused very little comment because of the limited circulation and life of the journal in which it was published. Holmes stoutly maintained that puerperal fever was not only contagious but that it was communicated by the doctor, either directly or indirectly. He said, "The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses." Holmes made the following rec-

ommendations: "A physician holding himself in readiness to attend cases of midwifery should never take any active part in postmortem examinations of puerperal fever cases. A physician present at such postmortems should use thorough ablution, change every article of dress and allow 24 hours to elapse before attending a case of midwifery. Similar precautions should be taken after the autopsy or surgical treatment of cases of erysipelas if the doctor is obliged to unite such duties with his obstetrical work which is in the highest degree inexpedient."

It was natural that such a damning indictment of the medical profession should sooner or later arouse opposition. Surely enough, a few years after Holmes' paper appeared, Hodge, who was professor of obstetrics at the University of Pennsylvania, and later Meigs, who was professor of obstetrics at the Jefferson Medical College, took strong exception to Holmes' statements and abused him personally. These two obstetricians were the leading authorities on obstetrics in the United States at the time and therefore their comments carried a great deal of weight with the doctors of this country. Holmes replied to the bitter criticisms leveled at him by reprinting his original article and giving new data to support his beliefs. He chose the following significant title for his second paper, "Puerperal Fever As a Private Pestilence." This paper demonstrates Holmes' masterful control of English, his clear and logical reasoning, and his generosity in giving credit to his predecessors who contributed to the subject of puerperal fever. In spite of the acrimony which characterized Hodges' and Meig's criticisms, Holmes maintained a reserved dignity and restraint of temper in his reply. After the publication of Holmes' second paper, many physicians accepted Holmes' ideas.

During the last few years there has been a great controversy as to who was the first to discover the cause of puerperal fever. An investigation of practically all great scientific discoveries will reveal that it is extremely rare for one man to make a significant scientific discovery alone without depending upon advances made by his predecessors or his contemporaries. Usually one man is given the credit for a great discovery, but it is generally the one who describes it most clearly and who persists in writing or talking about it until it is accepted. Puerperal infection has undoubtedly existed as long as mankind. References to it have been made by many ancient writers, but the English term puerperal fever is credited to Strother who used it in 1718. However, in 1676 Willis spoke of "febris puerperarum" which is the Latin equivalent.

In discussing the discoverers of the cause of puerperal fever, credit in this country is generally given to Oliver Wendell Holmes, whereas on the continent abroad, Semmelweis is accorded the honor of being the discoverer. However, the contagious nature of puerperal fever was known to Charles White in 1793, to Alexander Gordon in 1795, to Denman in 1801,

ART. V.—***The Contagiousness of Puerperal Fever.*** Read before the Boston Society for Medical Improvement, by OLIVER W. HOLMES, M.D., and published by request of the Society.

IN collecting, enforcing and adding to the evidence accumulated upon this most serious subject, I would not be understood to imply that there exists a doubt in the mind of any well-informed member of the medical profession as to the fact that puerperal fever is sometimes communicated from one person to another, both directly and indirectly. In the present state of our knowledge upon this point I should consider such doubts merely as a proof that the sceptic had either not examined the evidence, or, having examined it, refused to accept its plain and unavoidable consequences. I should be sorry to think with Dr. Rigby, that it was a case of "oblique vision;" I should be unwilling to force home the *argumentum ad hominem* of Dr. Blundell, but I would not consent to make a *question* of a momentous fact, which is no longer to be considered as a subject for trivial discussions, but to be acted upon with silent promptitude. It signifies nothing that wise and experienced practitioners have sometimes doubted the reality of the danger in question; no man has the right to doubt it any longer. No negative facts, no opposing opinions, be they what they may or whose they may, can form any answer to the series of cases now within the reach of all who choose to explore the records of medical science.

If there are some who conceive that any important end would be answered by recording such opinions, or by collecting the history of all the cases they could find in which no evidence of the influence of contagion existed, I believe they are in error. Suppose a few writers of authority can be found to profess a disbelief in contagion—and they are very few compared with those who think differently—is it quite clear that they formed their opinions on a view of all the facts, or is it not apparent that they relied mostly on their own solitary experience? Still further, of those whose names are quoted, is it not true that scarcely a single one could by any possibility have known the half or the tenth of the facts bearing on the subject which have reached such a frightful amount within the last few years? Again, as to the utility of negative facts, as we may briefly call them,—instances, namely, in which exposure has not been followed by disease,—although, like other truths, they may be worth knowing, I do not

Facsimile of title page of paper entitled "Contagiousness of Puerperal Fever."

to Armstrong in 1814, and to many other Englishmen long before Holmes and Semmelweis even thought about this disease. According to Peckham, the first American physician to write on the subject of puerperal fever was David Hosack of New York who said that puerperal fever was not infrequently highly contagious. In spite of the fact that these physicians recognized the contagious nature of puerperal fever, Holmes and Semmelweis fought hard to convince the medical profession of the truth of this. Holmes' efforts were almost entirely limited to his pen, but Semmelweis fought hard battles in his effort to convince his colleagues of the contagiousness of puerperal fever. He gave a clear definition of the disease showing conclusively that it is an infection of the genital wounds, he collected valuable clinica land pathological data, he gave experimental proof, and he showed the great value of prophylaxis. He fought bitterly to overcome the prejudices

against him and finally became insane. In spite of the fact that Semmelweis' first contribution did not appear until 1847 whereas Holmes' first paper was published in 1843, much more credit is generally given to Semmelweis for his efforts in spreading the truth about puerperal fever than to Holmes.

Holmes' essays on puerperal fever, as well as Semmelweis' contributions, were eventually fully accepted by the medical profession and resulted in an enormous reduction in the number of maternal deaths throughout the entire civilized world. Late in life Holmes said that his essays on puerperal fever gave him much more satisfaction than the poetry and prose he wrote throughout his long life. Among other statements concerning this, he said "When by the permission of Providence, I held up to the professional public the damnable facts connected with the conveyance of poison from one mother's chamber to another . . . for doing which humble office I desire to be thankful that I have lived, though nothing else shall ever come to life . . . I had to bear the sneers of those whose position I had assailed. . . ."

Holmes died peacefully at the age of 85 having retained the full vigor of his mind until the end. His loss was mourned not only by those interested in medicine and in literature, but also by all who were interested in the welfare of womankind. Throughout the world mothers have every reason to revere the memory of Oliver Wendell Holmes.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

A FORMIDABLE work[1] by Weiss and collaborators on diseases of the liver, biliary tract and pancreas consists of 1099 pages, printed on glossy paper and well illustrated with many photographs, diagrams, and X-ray plates, from the author's own and others' cases. There is an extensive list of references, covering 166 pages, and a subject and author's index. It is by far the most pretentious monograph by an American author that has appeared on the subject. In general it follows the influence of the German school; it is largely clinical, lacking perhaps in the presentation of the known fundamental physiological facts concerning the liver, bile ducts, gall bladder, and pancreas, required for a thorough understanding of the diseases of these organs from the point of view of the clinician. It is a "practical book," designed for the use of the medical student and practitioner, "devoted to the consideration of every day problems in biliary and pancreatic disease."

One chapter is devoted to the "indirect examination of the liver" by means of liver function tests, one to the examination of biliary tract contents after the manner of Lyon, one to the roentgenological examination of the organs considered, and one to the surgery of the liver, gall bladder, and bile ducts. The chapter devoted to parasitic diseases of the liver and gall bladder is, indeed, very well done and beautifully illustrated. The chapter on jaundice fails to clarify our understanding of the subject despite explanations, an involved classification, and a table of differential diagnosis of hematogenous and hepatogenous jaundice. Catarrhal jaundice, after the German style, is presented as a disturbance due to "catarrh" of the bile passages secondary to that of the gastro-intestinal tract. This origin is conceivable but now believed very rare. But scant attention is paid to the conception of catarrhal jaundice as a mild or abortive hepatitis involving the parenchymatous cells of the liver, which recent study would indicate is most frequently present.

The use of the term "portal hypertension," to which condition the author devotes a chapter, is interesting and unique. That a condition of hypertension exists within the portal system, similar to but independent of general arterial hypertension, as implied, is interesting if true. Most clinicians think of the condition described in terms of portal obstruction or stasis.

On the whole the volume is an interesting, instructive, comprehensive compilation on diseases of the liver, bile ducts, gall bladder, and pancreas, which will be appreciated by many practitioners.

CHARLES A. ELLIOTT.

THE impressive tome of 1581 pages—*Agents of Disease and Host Resistance*[2] by Gay represents a large and comprehensive undertaking. Part I, which may be regarded as an introduction to the book and an exposition of the author's concept of the cause of disease, treats of the general aspects of the causation, classification, and nature of disease. Part II deals with inanimate disease, agents as trauma, temperature, light, chemical poisons, etc., the tolerance of the organisms to them and the subjects anaphylaxis and allergy. Part III traces the history of bacteriology particularly in relation to disease and discusses the nature, form, structure, and physiology of micro-organisms and infection. Part IV covers infection in general and the principles of epidemiology. Part V has to do with resistance and immunity including a chapter on tissue immunity by the senior author whose research in this field is extensive and valuable. Part VI describes in detail the pathogenic bacteria and the diseases produced by them, Part VII the pathogenic spirochetes and spirochetoses, and Part VIII the pathogenic fungi and fungus diseases. Part IX under the heading "Indeterminate Pathogenic Forms and the Diseases Produced by Them" takes up the Rickettsia and filterable viruses with a chapter on the bacteriophage. Part X deals with the animal agents of disease the protozoa, helminths, and arthropods. Part XI is devoted to the diseases of obscure etiology which constitute approximately one-third of the total number of known diseases. Part XII discusses the practical application of bacteriological and immunological diagnostic reactions, active immunity through recovery and vaccination, serum prophylaxis and serum therapy and chemotherapy of bacterial and protozoan infections. From this outline, the breadth of scope and the fact that the contents of the book involve many branches of medicine is apparent.

The method of approach differs from the conventional in that instead of placing emphasis on particular agents or agencies the many agents together with the various secondary factors and host response

[1] DISEASES OF THE LIVER, GALL BLADDER, DUCTS AND PANCREAS: THEIR DIAGNOSIS AND TREATMENT. By Samuel Weiss, M.D., F.A.C.P. Chapter on SURGERY by J. Prescott Grant, M.C., F.A.C.S., M.R.C.S. Chapter on ROENTGENOLOGY by A. Judson Quimby, M.D., F.A.C.R. New York: Paul B. Hoeber, Inc., 1935.

[2] AGENTS OF DISEASE AND HOST RESISTANCE, INCLUDING THE PRINCIPLES OF IMMUNOLOGY, BACTERIOLOGY, MYCOLOGY, PROTOZOOLOGY, PARASITOLOGY AND VIRUS DISEASES. By Frederick P. Gay and collaborators. Springfield, Illinois, and Baltimore, Maryland: Charles C. Thomas, 1935.

are correlated and integrated to form a broad background for the presentation of disease causation. For the intimate knowledge required for the many phases of such an enterprise, the author is fortunate in the contributing authors all of whom, with the exception of four, have been associated with him in the same department. This has maintained better balance and continuity. Attention is centered on principles rather than practice, consequently detailed technical procedures are almost entirely omitted. The book is intermediate between a textbook and a system or collection of monographs. It is predicted that the volume will have an extensive use among specialists in infectious diseases, teachers, investigators, and practitioners and among graduate students. However, general medicine should find the book interesting and profitable, particularly Part I. The book is a rich mine of information.

A. A. Day.

THE sixth edition of *Preventive Medicine and Hygiene*[1] has been extensively rewritten and entirely reset. Many new subjects—such as contraception, maternal mortality, heart disease, diabetes, ringworm, snake bites, and psittacosis—have been added for the first time in this book. The discussions of venereal diseases, sex hygiene, heredity and eugenics, drug addiction, vitamins and the deficiency diseases, infant mortality, industrial hygiene and diseases of occupation, scarlet fever and undulant fever, have been extensively revised. Changed opinions have been withdrawn and each subject rewritten. The author has largely reorganized and added much new material to the subjects of tuberculosis, diphtheria, Vincent's angina, measles, insect borne diseases, flukes, quarantine, etc. The purpose of this, as of previous editions, is to meet the demand for an authoritative treatise based upon modern progress in hygiene and sanitation.

The book may be considered in two parts: first, that part which deals with the individual, and second, that part which deals with the environment of the individual.

The author's many years of varied experience in public health work, combined with the contributions of various authors in particular subjects, give this book the authoritative scientific basis from which can be secured accurate knowledge in the effort to prevent disease and maintain health.

Clifford J. Barborka.

[1] Preventive Medicine and Hygiene. By Milton J. Rosenau. 6th ed. New York and London: D. Appleton-Century Co., 1935.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

A Glasgow Manual of Obstetrics. By Samuel J. Cameron, M.B., F.R.F.P.S., F.C.O.G., John Hewitt, M.B., Ch.B., F.C.O.G., Robert A. Lennie, M.D., F.R.F.P.S., F.C.O.G., Ellen D. Morton, M.B., Ch.B., M.C.O.G. 2d ed. London: Edward Arnold & Co., 1936.

A Textbook of Obstetrics; for Students and Practitioners. By Frederick C. Irving, A.B., M.D., F.A.C.S. New York: The Macmillan Co., 1936.

The Phenomena of Life; a Radio-Electric Interpretation. By George Crile. New York: W. W. Norton & Co., Inc., 1936.

Oxford Medical Publications. The Tuberculin Handbook. By Halliday Sutherland, M.D. London: Oxford University Press, 1936.

La Sinfisiotomia en Espana. By Dr. Angel Guerrero Abellan. Barcelona, Spain, 1936.

Those Were Good Days! By Carl Ludwig Schleich. Translated by Bernard Miall. New York: W. W. Norton & Co., 1936.

A Textbook of Roentgenology; The Roentgen Ray in Diagnosis and Treatment. By Bede J. Michael Harrison, M.B., Ch.M., D.M.R.E.(Cantab.), F.A.C.R. Baltimore: William Wood & Co., 1936.

Post-Graduate Surgery. Edited by Rodney Maingot, F.R.C.S. (Eng.). With an Introduction by The Right Hon. Lord Moynihan of Leeds, K.C.M.G., C.B., M.S., F.R.C S. Vol. 1. New York: D. Appleton-Century Co. Inc., 1936.

An Introduction to Surgery. By Rutherford Morison, M.D., F.R.C.S. Edin., F.R.C.S. Eng., M.A., D.C.L., LL.D., and Charles F. M. Saint, C.B.E., M.D., M.S., F.R.C.S., F.R.A.C.S. 3d ed. Baltimore: William Wood & Co., 1935.

The True Physician. The Modern "Doctor of the Old School." By Wingate M. Johnson, M.D. New York: The Macmillan Co., 1936.

A Textbook of Surgery. By American Authors. Edited by Frederick Christopher, B.S., M.D., F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1936.

An Index of Differential Diagnosis of Main Symptoms. By Various Writers. Edited by Herbert French, C.V.O., C.B.E., M.A., M.D. Oxon., F.R.C.P. Lond. 5th ed. Baltimore: William Wood and Co., 1936.

AMERICAN COLLEGE OF SURGEONS

LIBRARY AND DEPARTMENT OF LITERARY RESEARCH, AMERICAN COLLEGE OF SURGEONS

IRVIN ABELL, M.D., F.A.C.S., LOUISVILLE, KENTUCKY
Chairman, Committee on the Library

THE gradual, well-rounded development of the Library of the American College of Surgeons and the many calls upon its facilities on the part of the Fellows of the College and other members of the medical profession is a source of gratification to the Committee on the Library. The Library, established with the well-chosen collection of the late John B. Murphy as a nucleus, has been augmented during the past fifteen years by additional interesting and valuable collections. Outstanding among these are the volumes from the Albert J. Ochsner collection of bound journals and textbooks, presented through the courtesy of the Augustana Hospital, and the volumes of historic interest which, together with the pictures and mementoes of his life and work, were placed in the Albert J. Ochsner Memorial Room by the late Mrs. Ochsner.

The William McDowell Mastin and the H. Winnett Orr collections likewise contain volumes of historic interest. The former is especially rich in eighteenth and nineteenth century monographs and the latter, consisting of approximately four hundred volumes, includes a rare Galen (1633), a Paré (1579), Boerhaave's *Opera Omnia Medica Complectentia*, and other museum pieces. A catalogue of the Orr collection is being prepared by the donor and will undoubtedly prove an interesting and valuable historical study in the field of general and orthopedic surgery.

Many individual volumes and smaller collections have been received from time to time. Dr. G. P. Coopernail has presented a small volume, *Sententiae Omnes*, by Francisco Venerio (1555), a volume containing the handwritten notes to the third edition of Emmet's *Principles and Practice of Gynaecology*, and the pamphlet entitled *Dr. Wells, the Discoverer of Anaesthesia*. Among the present day studies are to be found the beautifully illustrated limited editions by Nolie Mumey entitled *William Beaumont: the Centenary of the Publication of His Contributions to Medicine* and *Silas Weir Mitchell: the Versatile Physician*.

The more extensive contributions to the general reference library include the journal files of the late Albert Van der Veer and the unique, fifty-volume collection of the late H. W. Mills on hydatid cysts. The reference library likewise contains an extensive and valuable collection of current textbooks and monographs, and representative surgical journals of the world, American, Canadian, British, Australian, Mexican, South American, and Continental, which, together with the collections available through neighboring university and private libraries, makes possible the research service offered by the Department of Literary Research.

Many are accustomed to think of a library only in terms of immediate availability to personal visitation; desirable as this opportunity may be the lack of it does not interfere with the acquisition of data and knowledge comprised in the world of surgical literature. The staff of the College Library welcomes both the personal visits of the Fellows and, as well, their requests by mail or wire for specific material in which they may be interested.

The staff of workers maintained to care for these requests is equipped to select material of interest from the extensive reprint files (package library service) and to compile bibliographies, prepare abstracts and translations on any medical or surgical subject. The package library file includes approximately 90,000 pamphlets and permits of a prompt response to each request, data being furnished within a few hours' time if need be. However, the package library does not afford a complete review of a subject. When a complete study is desired the package library should be supplemented by a bibliography and translations of the important articles upon the subject, with notes or brief abstracts of those of lesser interest. The Department of Literary Research, maintaining on its staff workers trained in this field, is well

equipped to furnish this more complete service. The personnel includes full-time workers experienced in translating from the German, French, Italian, Spanish, Dutch, and Scandinavian languages and associated workers in the Bohemian, Russian, and Hungarian languages. It is thus prepared to meet practically any language requirement which may arise. Brochures descriptive of the plan of the Department, and blanks to facilitate the placing of inquiries are furnished upon request.

Today the research field marks the zone of advance in the development of surgical knowledge, its gleanings being harvested by the laboratory worker and the clinical observer. For the vast majority of surgeons engaged in private practice, as are the Fellows of the College, clinical research and priority achievement constitute the greatest means of adding to the sum total of surgical attainment. A complete bibliography prepared by the Department of Literary Research with abstracts and translations of all articles presented in the polyglot literature of the world is a study of great value to such persons. An analysis will reveal similar or comparable experiences, the value of laboratory data, the opportunity of comparing pathological findings, the contrast of diverse treatments with therapeutic results, and a more or less correct evaluation of all the clinical factors. A study conducted along such lines acquires a definite value and an accredited position in surgical literature and the Department of Literary Research has spared no pains in making its program along this line both helpful and complete.

It is the hope of the Committee on the Library that Fellows of the College and other members of the profession will continue in increasing numbers to take advantage of the facilities which the Library offers to the end that one of the objectives of the College, namely, increase in and dissemination of surgical knowledge may be more widely attained. The Library is the property of the Fellows of the College and a sense of possession should stimulate them to use it to their own advancement: in so doing they would be conscious of raising the level of surgical practice and adding to the Science and Art of Surgery.

THE 1936 CLINICAL CONGRESS IN PHILADELPHIA

FOR the twenty-sixth annual Clinical Congress of the American College of Surgeons to be held in Philadelphia, October 19–23, 1936, the surgeons of that great medical center have organized under the leadership of a strong and representative committee, and are planning to provide a program of surgical clinics and demonstrations that will present a complete showing of their clinical activities in all departments of surgery. The Executive Committee in charge of arrangements is as follows: Henry P. Brown, chairman; Gilson C. Engel, secretary; Francis H. Adler, Dorothy C. Blechschmidt, John O. Bower, L. K. Ferguson, Bruce L. Fleming, Karl M. Houser, Robert H. Ivy, H. P. Leopold, Richard H. Meade, Jr., Frank Mogavero, John R. Moore, E. A. Mullen and Louis C. Scheffey. The Committee is assured of the hearty co-operation of the clinicians at the five medical schools and more than thirty hospitals that will participate in the clinical program.

A preliminary schedule of operative clinics and demonstrations is being prepared by the Committee for publication in an early issue of SURGERY, GYNECOLOGY AND OBSTETRICS. Clinics will be arranged for the afternoon of Monday, October 19, and for the mornings and afternoons of each of the four following days. All departments of surgery will be represented in the program—general surgery, gynecology and obstetrics, genito-urinary surgery, neurosurgery, orthopedics, proctology, and surgery of the eye, ear, nose and throat.

The Executive Committee of the Board of Regents is preparing programs for the five evening sessions. At the presidential meeting on Monday evening, the first formal session of the Congress, the retiring president, Dr. Donald C. Balfour, will deliver his address. The president-elect, Dr. Eugene H. Pool, will deliver his inaugural address at the convocation on Friday evening, on which occasion the 1936 class of initiates will be received into Fellowship. At sessions on Tuesday, Wednesday, and Thursday evenings eminent surgeons of the United States and Canada together with visiting surgeons from foreign countries will present and discuss papers dealing with surgical subjects of timely importance.

In addition to an extensive schedule of operative clinics and demonstrations at the hospitals, the sub-committee on ophthalmology and otolaryngology is preparing a series of clinical demonstrations to be held daily in the ballroom of the Bellevue-Stratford Hotel to be given by visiting ophthalmologists and otolaryngologists.

The Committee on Arrangements expects to emphasize certain special features in the clinical program including (1) fracture clinics, demonstrating modern methods in the treatment of fractures; (2) cancer clinics, demonstrating the treatment of cancer by surgery, radium and X-ray; (3) clinics in traumatic surgery for the presentation of the newer methods of rehabilitation of the injured by surgery and physical therapy.

Other features of this year's Congress include a conference on fractures under the auspices of the Committee on Fractures, a cancer symposium arranged by the Committee on the Treatment of Malignant Diseases, and a conference on industrial medicine and traumatic surgery under the auspices of the Committee on Industrial Medicine and Traumatic Surgery.

The showing of films demonstrating clinical features of interest has met with popular acceptance in recent years and will be continued at this session with an enlarged program of surgical films, both sound and silent, to be exhibited daily at headquarters.

Following its established custom and in recognition of an obligation to the public to provide authoritative information on modern surgery, better hospitals, and the prevention of disease, a community health meeting will be held Wednesday evening in the Municipal Auditorium under the auspices of the College.

The annual hospital conference will open the Congress with a session in the ballroom of the Bellevue-Stratford Hotel at 10 o'clock on Monday morning. An interesting program of papers, round table conferences, and practical demonstrations dealing with problems related to hospital efficiency is being prepared for sessions on Monday, Tuesday, Wednesday, and Thursday. A greatly increased interest on the part of surgeons in both the administrative and scientific phases of hospital work has been evidenced in recent years and the program of this year's conference will provide for discussions of subjects of interest to the three major hospital groups—medical, surgical, and administrative. It is proposed to make this year's program of wide interest and practical character through a careful selection of subjects to be presented and discussed by surgeons and hospital executives, particular emphasis being directed toward professional standards

and the vital problems related to hospital economics.

Headquarters for the Congress will be established at the Bellevue-Stratford Hotel where the grand ballroom, Garden, Clover, and Red Rooms and other large rooms on the first and second floors have been reserved for scientific sessions and conferences, registration and clinic ticket bureaus, bulletin boards, executive offices, etc. Thus the activities of the Congress will be centralized under one roof.

The Technical Exhibition will be located in the large rooms on the first and second floors adjacent to the ballroom. The registration and clinic ticket bureau, together with the information desk, will be centrally located as regards the exhibit rooms in which will be placed the bulletin boards on which the daily clinical program will be posted each afternoon. Leading manufacturers of surgical instruments, X-ray apparatus, operating room lights, hospital apparatus and supplies of all kinds, ligatures, dressings, pharmaceuticals and publishers of medical books will be represented in this exhibition.

We are assured that the railways of the United States and Canada will grant reduced rates for the Clinical Congress in Philadelphia, and negotiations for such fares are in progress with the various railway traffic associations.

The hospitals and medical schools of Philadelphia afford accommodations for a large number of visiting surgeons, but to insure against overcrowding, attendance at the Congress will be limited to a number that can be comfortably accommodated at the clinics, the limit of attendance being based upon the result of a survey of the amphitheaters, operating rooms, and laboratories of the hospitals and medical schools to determine their capacity for visitors. It is expected, therefore, that those surgeons who wish to attend the Congress will register in advance.

Admittance to clinics and demonstrations will be controlled by means of special clinic tickets, such plan providing an efficient means for the distribution of the visiting surgeons among the several clinics and insuring against overcrowding, as the number of tickets issued for any clinic will be limited to the capacity of the room in which that clinic is given.

A registration fee of $5.00 is required of each surgeon attending the annual Clinical Congress, such fees providing the funds with which to meet the expenses of the meeting. To each surgeon registering in advance a formal receipt for the registration fee is issued, which receipt is to be exchanged for a general admission card upon his registration at headquarters. This card, which is non-transferable, must be presented in order to secure clinic tickets and admission to the evening meetings.